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Patent- og Varemærkestyrelsen
Kongeriget Danmark

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PATENT- OG VAREMÆRKESTYRELSEN

NOVEL COMPOUNDS FOR TREAMENT OF OBESITY

FIELD OF THE INVENTION

The invention relates to novel hydroxyl styrene sulfonyl derivatives, to their use in therapy, to pharmaceutical compositions comprising said derivatives, to the use of said derivatives in the manufacture of medicaments, and to therapeutic methods comprising the administration of said derivatives to a patient. The compounds exert an uncoupling activity and are useful in the treatment of obesity.

BACKGROUND OF THE INVENTION

Obesity is a well-known risk factor for the development of many very common diseases such as atherosclerosis, hypertension, type 2 diabetes (non-insulin dependent diabetes mellitus (NIDDM)), dyslipidemia, coronary heart disease, and osteoarthritis and various malignancies. It also causes considerable problems through reduced motility and decreased quality of life. The incidence of obese people and thereby also these diseases is increasing throughout the entire industrialised world.

The term obesity implies an excess of adipose tissue. In this context obesity is best viewed as any degree of excess adiposity that imparts a health risk. The cut off between normal and obese individuals can only be approximated, and the health risk imparted by the obesity is probably a continuum with increasing adiposity. In the context of the present invention, individuals with a body mass index (BMI = body weight in kilograms divided by the square of the height in meters) above 25 are to be regarded as obese

Even mild obesity increases the risk for premature death and conditions such as diabetes, dyslipidemia, hypertension, atherosclerosis, gallbladder disease and certain types of cancer. In the industrialised western world the prevalence of obesity has increased significantly in the past few decades. Because of the high prevalence of obesity and its health consequences, its prevention and treatment should be a high public health priority.

Except for exercise, diet and food restriction, which is not feasible for a vast number of patients, no convincing treatment for reducing body weight effectively and acceptably currently exist. However, not only in view of the considerable problems directly related to obesity as described above, but also due to the important effect of obesity as a risk factor in serious and even mortal and common diseases, it is important to find pharmaceutical compounds which are useful in prevention and/or treatment of obesity.

When energy intake exceeds expenditure, the excess calories are stored predominately in adipose tissue, and if this net positive balance is prolonged, obesity results, i.e. there are two components to weight balance, and an abnormality on either side (intake or expenditure) can lead to obesity. This process may be counteracted by increasing the energy expenditure (for instance via exercise) or decreasing the energy intake (for instance by dieting). Pharmacological treatment available up to date only consists of Sibutramine (acting via serotonergic mechanisms, Abbott) and Orlistat (reducing fat uptake from the gut, Roche Pharm). There is therefore a need for pharmaceutical compounds which may be useful in prevention and/or treatment of obesity, for instance by increasing the energy expenditure or decreasing the energy intake.

One way of increasing energy expenditure is by increasing the metabolic rate. By the oxidative phosphorylation in mitochondria, the energy from glucose metabolism and free fatty acids oxidation is used to drive the phosphorylation of ADP to ATP. When NADH and $FADH_2$ formed in the TCA cycle are oxidised back to NAD^+ and FAD respectively, protons are pumped out of the mitochondrial matrix. The resulting pH gradient (matrix pH~8 and outside pH~7) and potential (~-170 mV, inside negative) across the inner mitochondrial membrane constitute the electrochemical proton gradient. As the effect of a one-unit pH difference corresponds to a potential of 61.5mV, the electrochemical proton gradient exerts a protonmotive force of roughly -230 mV, which is the driving force for the mitochondrial ATP synthesis.

When the ATP consumption increases, the cells respond by increasing the ATP synthesis and consequently the inward flux of protons through the ATP synthase, the enzyme responsible for ATP synthesis and thereby the metabolic rate is increased. Chemical uncouplers are compounds, which can transport protons across membranes, and when protons are transported across the inner mitochondrial membrane, the ATP synthase is bypassed. At the (alkaline) matrix side the proton is released and the deprotonated uncoupler returns to the inter-membrane space where it picks up another proton. The cycling of the uncoupler (or ATP synthesis) and the resulting proton transport leads to an increased outward pumping of protons through an increased oxidation of NADH and $FADH_2$ by the respiratory chain. The NADH concentration in the matrix will consequently drop. Since NADH feed-back inhibits three steps in the TCA cycle (NADH is the main regulator of the TCA cycle), the flux through the TCA cycle will increase. Hence, the metabolic rate increases.

Compounds, such as chemical uncouplers, which act by increasing the metabolic rate may thus be useful for treating obesity, but also for treating other conditions such as atherosclerosis, hypertension, diabetes, especially type 2 diabetes (NIDDM (non-insulin de-

pendent diabetes mellitus)), dyslipidemia, coronary heart disease, gallbladder disease, osteoarthritis and various types of cancer such as endometrial, breast, prostate and colon cancers and the risk for premature death as well as diseases which are closely connected to obesity, and conditions which are improved by a reduced mitochondrial potential.

Furthermore, chemical uncouplers may reduce reactive oxygen species (ROS) that are assumed (De Grey et al, Eur J. Biochem 269, 1995 ff (2002)) to be involved in the aging process, in damage of heart tissue as well as neuronal tissue. It is therefore also possible that conditions affected by ROS may be reversed or halted by intervention of chemical uncouplers.

The best known chemical uncoupler is 2,4-dinitrophenol (DNP), which has been shown to increase energy expenditure in humans as well as animals. The side effects at higher doses include increased perspiration, increased body temperature, vasodilatation, skin rashes, cataracts, neuritis and death! Two fatalities amongst the first 100.000 persons treated with DNP, and the fact that the lowest dose, which could be lethal, is only twice the average dose giving a desired 50% increase in basal metabolic rate giving a very narrow safety window, combined with other factors led to the removal of DNP from the market. Since then nobody have attempted to develop or market uncouplers for the treatment of obesity.

DNP is the best known chemical uncoupler; but many other compounds are known to induce uncoupling. DNP derivatives such as 4,6-dinitro-*o*-cresol (Victoria Yellow) and 2,4-dinitro-1-naphtol (Martius Yellow) as well as structurally unrelated compounds such as 2,6-di-t-butyl-4-(2',2'-dicyanovinyl)phenol) (SF6847) (also known as 2-(3,5-di-tert-butyl-4-hydroxybenzylidene)-malononitrile), carbonylcyanide m-chlorophenylhydrazone (CCCP) and carbonylcyanide *p*trifluoromethoxy-phenylhydrazone (FCCP) (Miyoshi H et al. Quantitative releationship between protenophoric and uncoupling activities of analogs of SF6847 (2,6-di-t-butyl-4-(2',2'-dicyanovinyl)phenol), Biochimica et Biophysica Acta 891, 293-299 (1987)) are uncouplers.

Another class of chemical uncouplers is the salicylanilides of which S-13 is the most potent compound discovered so far (Terada H et al. Structural Requirements of Salicylanilides for Uncoupling Activity in Mitochondria Quantitative Analysis of Structure- Uncoupling Relationships, Biochimica et Biophysica Acta 936, 504-512 (1988)).

Goto K et al, Chem. Pharm. Bull. 44(3), 547-551 (1996) describes diethyl 4-[(4-bromo-2-cyanophenyl)carbamoyl]-benzylphosphonate for use as an LPL activator.

T. Shimokawa et al, Drug Development Research 51(1), 43-48 (2000) describes 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxy-3-methylbenzamide for use as a glucose uptake stimulator.

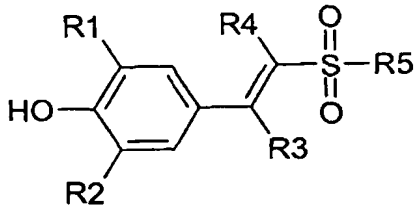
WO00/06143 to Texas Pharmaceuticals Inc. relates to a method for inducing intracellular hyperthermia comprising a step of administering a mitochondrial uncoupling agent, such as 2,4-dinitrophenol.

US 4,673,691 to Bachynsky relates to the use of 2,4-dinitrophenol for treating obesity.

Hydroxy styrene sulfonyl derivatives have been reported to exert a variety of activities. As examples, US 5,792,771 discloses hydroxy styrene sulfonyl derivatives as modulators of tyrosine kinase signal transduction, and WO 96/40629 discloses hydroxy styrene sulfonyl derivatives as useful in the treatment of cell proliferative disorders.

SUMMARY OF THE INVENTION

The present inventors have surprisingly found that compounds of formula I are potent chemical uncouplers. Accordingly, the invention relates to compounds of formula I



[I]

wherein each R1 and R2 independently represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, haloalkyl, alkoxy, alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6
-OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;

R3 represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, alkoxy ,alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6, -OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;

R4 represents nitro, cyano, halogen, haloalkyl, -C(O)R6, -C(O)OR6, -$C(O)N(R6)_2$ or –$S(O)_2$OR6, $S(O)_n$R6, $S(O)_2N(R6)_2$
-$P(O)(OR6)_2$ or –$B(OR6)_2$;

R6 represents hydrogen or alkyl, aryl or heteroaryl, all of which may be substituted with one or more substituent selected from amongst hydroxyl, halogen, nitro and cyano;

n represents 0, 1 or 2;

R5 represents alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, all of which are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, carboxyl, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-

R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -NR7-C(O)R7, NR7-S(O)$_n$R7,
-$(CH_2)_p$-N(R7)(R8) and phenyl, said phenyl being optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, nitro, O-R13, -S(O)$_n$R11, -O-C(O)R11, -C(O)-O-R11, -C(O)-R11 -C(O)-N(R11)(R12), -N(R11)(R12), -$(CH_2)_p$-N(R11)-C(O)-R12, -B(OR11)(OR12), -$(CH_2)_p$-O-R11, -$(CH_2)_p$-N(R11)(R12) ;

R7 and R8 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, dialkylether, cycloalkyl, heterocyclyl or phenyl, wherein said phenyl and heterocyclyl are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyl, hydroxyalkyl, cyano, nitro, -N(R9)(R10) and –$(CH_2)_p$-N(R9)(R10);

R9 and R10 independently represent hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl or cycloalkyl;

or R4 and R5 together with the atoms to which they are attached constitute a 5, 6, 7 or 8 membered ring, which may be saturated, either partly or fully or unsaturated, and wherein said ring is optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano and nitro;

each R11 and R12 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl or phenyl;

R13 represents haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalyl;

p represents 0, 1 or 2;

with the proviso that if R5 represents phenyl, then said phenyl is substituted, however not by fluor or trifluoromethyl; and with the proviso that R5 does not represents cyanomethyl; and with the further proviso that if R5 is thienyl or pyridyl, then said thienyl or pyridyl is substituted;

and pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof.

The present invention also relates to the use of compounds of formula I in therapy, and in particular to pharmaceutical compositions comprising said compounds.

In another aspect, the invention relates to therapeutic methods comprising administering a therapeutically effective amount of a compound of formula I to a patient to a patient in need thereof.

In a still further aspect, the invention relates to the use of compounds of formula I in the manufacture of medicaments.

DEFINITIONS

In the present context, the term "alkyl" is intended to indicate a straight or branched chain saturated monovalent hydrocarbon radical having from one to twelve carbon atoms, also denoted as C_{1-12}-alkyl. Typical alkyl groups are alkyl groups with from one to eight or from one to six carbon atoms, also denoted as C_{1-8}-alkyl and C_{1-6}-alkyl respectively. Typical C_{1-6}-alkyl groups include, but are not limited to e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 4-methylpentyl, n-pentyl, n-hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl (neopentyl), 1,2,2-trimethylpropyl and the like, while typical C_{1-8}-alkyl groups include the same groups as well as alkyl groups having seven or eight carbon atoms, such as heptyl, octyl, 2,2-dimethylhexyl and the like. The term "C_{1-6}-alkyl" as used herein also includes secondary C_{3-6}-alkyl and tertiary C_{4-6}-alkyl. The term "C_{1-8}-alkyl" as used herein also includes secondary C_{3-8}-alkyl and tertiary C_{4-8}-alkyl. The term "C_{1-12}-alkyl" as used herein also includes secondary C_{3-12}-alkyl and tertiary C_{4-12}-alkyl.

In the present context, the term "alkenyl" is intended to indicate a straight or branched chain monovalent hydrocarbon radical having from two to six carbon atoms and at least one carbon-carbon double bond, for example C_{3-5}-alkenyl. Typical C_{3-5}-alkenyl groups include vinyl, allyl, 1-propenyl, 1,3 butadiene-1-yl, and the like. The term "conjugated alkenyl" as used herein, alone or in combination, refers to an alkenyl having consecutive double bonds, such as for instance 1,3 butadiene-1-yl.

In the present context, the term "alkynyl" is intended to indicate a straight or branched chain monovalent hydrocarbon radical having from two to six carbon atoms and at least one carbon-carbon triple bond and optionally one or more carbon-carbon double bonds. Examples include ethynyl, propynyl and 3,4-pentadiene-1-ynyl.

The term "halogen" is intended to indicate members of the seventh main group of the periodic system, *i,e,* fluoro, chloro, bromo and iodo.

In the present context, the term "dialkylether" is intended to indicate a compound of the formula –R'-O-R', wherein each R' independently represent alkyl as indicated above. Examples of dialkylether include dimethyl-ether, methylethyl-ether and diethylether.

In the present context, the term "aryl" is intended to indicate a carbocyclic aromatic ring radical or a fused aromatic ring system radical wherein at least one of the rings are aromatic. Typical aryl groups include phenyl, biphenyl, naphtyl, and the like.

The term "heteroaryl", as used herein, alone or in combination, refers to an aromatic ring radical with for instance 5 to 7 member atoms, or to a fused aromatic ring system radical with for instance from 7 to 18 member atoms, wherein at least on ring is aromatic, containing

one or more heteroatoms selected from nitrogen, oxygen, or sulfur heteroatoms, wherein N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions. Examples include furanyl, thienyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrazinyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, and indazolyl, and the like. Examples of "aryl" and "heteroaryl" include phenyl, biphenyl, indenyl, fluorene, naphthyl (1-naphthyl, 2-naphthyl), anthracenyl (1-anthracenyl, 2-anthracenyl, 3-anthracenyl), thienyl (2-thienyl, 3-thienyl), furanyl (2-furanyl, 3-furanyl), indolyl, oxadiazolyl, isoxazolyl, thiadiazolyl, oxatriazolyl, thiatriazolyl, quinazolinyl, fluorenyl, xanthenyl, isoindanyl, benzhydryl, acridinyl, thiazolyl, pyrrolyl (1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl), pyrazolyl (1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-4-yl 1,2,3-triazol-5-yl, 1,2,4-triazol-3-yl, 1,2,4-triazol-5-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (isoxazo-3-yl, isoxazo-4-yl, isoxaz-5-yl), isothiazolyl (isothiazo-3-yl, isothiazo-4-yl, isothiaz-5-yl) thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), pyridinyl (2-pyridinyl, 3-pyridinyl, 4-pyridinyl), pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3- pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolinyl (2-quinolinyl, 3-quinolinyl, 4-quinolinyl, 5-quinolinyl, 6-quinolinyl, 7-quinolinyl, 8-quinolinyl), isoquinolinyl (1-isoquinolinyl, 3-isoquinolinyl, 4-isoquinolinyl, 5-isoquinolinyl, 6-isoquinolinyl, 7-isoquinolinyl, 8-isoquinolinyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydrobenzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzob]furanyl), 7-(2,3-dihydro-benzo[b]furanyl)), benzo[b]thiophenyl (benzo[b]thiophen-2-yl, benzo[b]thiophen-3-yl, benzo[b]thiophen-4-yl, benzo[b]thiophen-5-yl, benzo[b]thiophen-6-yl, benzo[b]thiophen-7-yl), 2,3-dihydro-benzo[b]thiophenyl (2,3-dihydro-benzo[b]thiophen-2-yl, 2,3-dihydrobenzo[b]thiophen-3-yl, 2,3-dihydro-benzo[b]thiophen-4-yl, 2,3-dihydro-benzo[b]thiophen-5-yl, 2,3-dihydro-benzo[b]thiophen-6-yl, 2,3-dihydro-benzo[b]thiophen-7-yl), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), indazolyl (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (2-benzoxazolyl, 3-benzoxazolyl, 4-benzoxazolyl, 5-benzoxazolyl, 6-benzoxazolyl, 7-benzoxazolyl), benzothiazolyl (2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepinyl (5H-

dibenz[b,f]azepin-1-yl, 5H-dibenz[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz[b,f]azepine-4-yl, 5H-dibenz[b,f]azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepinyl (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), benzo[1,3]dioxole (2-benzo[1,3]dioxole, 4-benzo[1,3]dioxole, 5-benzo[1,3]dioxole, 6-benzo[1,3]dioxole, 7-benzo[1,3]dioxole), and tetrazolyl (5-tetrazolyl, N-tetrazolyl).

The term "fused aromatic ring system" as used herein, alone or in combination, refers to a carbocyclic aromatic ring radical fused to another carbocyclic or heterocyclic ring radical, the two rings having two atoms in common. Typical fused aromatic ring systems include, but are not limited to napthalene, quinoline, isoquinoline, indole, and isoindole.

In the present context the term "cycloalkyl" is intended to indicate a cyclic saturated monovalent hydrocarbon radical having 3, 4, 5, 6, 7 or 8 ring carbon atoms.

The term "hetorocyclyl" is intended to indicate a cyclic non-aromatic radical having 5, 6, 7 or 8 ring atoms, wherein at least one ring atom is selected from the group consisting of nitrogen, oxygen and sulfur heteroatoms, wherein N-oxides and sulfur monoxides and sulfur dioxides are permissible heterocyclic substitutions. Examples of heterocycles include tetrahydrofuran, 1,4-dioxane, 1,3-dioxane, piperidine, pyrrolidine, morpholine and piperazine.

In the present context, the term "alkoxy" is intended to indicate a radical of the formula –OR', wherein R' represents alkyl as indicated above.

In the present context, the term "alkylamino" is intended to indicate a radical of the formula –NH-R' or $-N(R')_2$, wherein each R' represents alkyl as indicated above.

The term "nitro" shall mean the radical $-NO_2$.

The term "cyano" shall mean the radical -CN.

In the present context, the term "haloalkyl" is intended to indicate an alkyl, as defined above, substituted with one or more halogens, as defined above. Examples include trihalomethyl, such as trifluoromethyl and trichloromethyl, and 2,2,2-trichloro-1-ethyl.

In the present context, the term "hydroxyalkyl" is intended to indicate an alkyl, as defined above, substituted with one or more hydroxyl groups. Examples include hydroxymethyl, 1-hydoxy-1-ethyl and 2-hydroxy-1-ethyl.

As used herein, the term "solvate" is a complex of variable stoichiometry formed by a solute (in casu, a compound according to the present invention) and a solvent. Solvents may be, by way of example, water, ethanol, or acetic acid.

As used herein, the term "prodrug" includes biohydrolyzable amides and biohydrolyzable esters and also encompasses a) compounds in which the biohydrolyzable functional-

ity in such a prodrug is encompassed in the compound according to the present invention, and b) compounds which may be oxidized or reduced biologically at a given functional group to yield drug substances according to the present invention. Examples of these functional groups include 1,4-dihydropyridine, N-alkylcarbonyl-1,4-dihydropyridine, 1,4-cyclohexadiene, tert-butyl, and the like.

As used herein, the term "biohydrolyzable ester" is an ester of a drug substance (in casu, a compound according to the invention) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties *in vivo* such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is, for example increased solubility or that the biohydrolyzable ester is orally absorbed from the gut and is transformed to a compound according to the present invention in plasma. Many examples of such are known in the art and include by way of example lower alkyl esters (*e.g.*, C_1-C_4), lower acyloxyalkyl esters, lower alkoxyacyloxyalkyl esters, alkoxyacyloxy esters, alkyl acylamino alkyl esters, and choline esters.

As used herein, the term "biohydrolyzable amide" is an amide of a drug substance (in casu, a compound according to the present invention) which either a) does not interfere with the biological activity of the parent substance but confers on that substance advantageous properties in vivo such as duration of action, onset of action, and the like, or b) is biologically inactive but is readily converted in vivo by the subject to the biologically active principle. The advantage is, for example increased solubility or that the biohydrolyzable amide is orally absorbed from the gut and is transformed to a compound according to the present invention in plasma. Many examples of such are known in the art and include by way of example lower alkyl amides, α-amino acid amides, alkoxyacyl amides, and alkylaminoalkylcarbonyl amides.

In the present context, the term "pharmaceutically acceptable salt" is intended to indicate salts which are not harmful to the patient. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-

aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like.

A "therapeutically effective amount" of a compound as used herein means an amount sufficient to cure, alleviate or partially arrest the clinical manifestations of a given disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.

The term "treatment" and "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relief the symptoms and complications, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. The patient to be treated is preferably a mammal, in particular a human being, but it may also include animals, such as dogs, cats, cows, sheep and pigs.

DESCRIPTION OF THE INVENTION

In one embodiment, each R1 and R2 are independently selected from the list consisting of alkyl, aryl, heteroaryl, halogen, nitro, -C(O)OR6, -$S(O)_2$OR6, in particular R1 and R2 independently represents alkyl, halogen or nitro. Specific examples of R1 and R2 include C_{1-6}alkyl, such as tert.-butyl, butyl, isopropyl or methyl, nitro, chloro, bromo and iodo.

In a further embodiment, R3 represents hydrogen, alkyl, alkenyl, alkynyl, alkoxy or alkylamino. In particular, R3 may represent C_{1-4}alkyl, such as methyl.

In a further embodiment, R4 represents nitro, cyano, -C(O)R6, -C(O)OR6, $-S(O)_2OR6$, -$C(O)N(R6)_2$, $-S(O)_nR6$ or $S(O)_2N(R6)_2$ wherein n represents 1 or 2.

In a still further embodiment of the invention, R4 and R5 together with the atoms to which they are attached constitute a 5 or 6 membered ring, which may be saturated, either partly or fully, or unsaturated, and wherein said ring is optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano and nitro. Examples of said rings are [1,3]Dithiolane 1,1,3,3-tetraoxide, 1,1-Dioxo-tetrahydro-1-thiophen-3-one, 1,1-Dioxo-thiazolidine-4-one, 1,1-Dioxo-thiomorpholine-3-one tetrahydrothiopyran-1,1-dioxide and tetrahydrothiophen-1,1-dioxide.

In a still further embodiment, R5 represents alkyl alkenyl, aryl, heteroaryl, heterocyclyl, all of which are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, haloalkyl, -O-R7, $-S(O)_nR7$, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), $-(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), $-(CH_2)_p$-O-R7, $-(CH_2)_p$-N(R7)(R8), -NR7-C(O)R7, $-NR7-S(O)_n$-R7. In particular, R5 may represent methyl or 2-propanyl, optionally substituted with a substituent selected from the list consisting of halogen, hydroxyl, cyano, nitro, -C(O)-O-R7, -C(O)-N(R7)(R8).

In one embodiment, R5 represents aryl, and in particular phenyl, optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, haloalkyl, -O-R7, $-S(O)_nR7$, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), $-(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), $-(CH_2)_p$-O-R7, $-(CH_2)_p$-N(R7)(R8), -NR7-C(O)R7, $-NR7-S(O)_n$-R7. In a particular embodiment, said substituents are selected amongst, chloro, hydroxyl, cyano, carboxyl, nitro, NR7R8, -O-R7, C(O)-R7, -C(O)-O-R7, -C(O)-N(R7)(R8). Specific examples of said substituents include chloro, carboxyl, nitro, trifluoromethoxy, N,N-bis(2-methoxy-ethyl)-carbonyl, dimethylaminecarbonyl, N,N-bis(2-hydroxypripyl)-carbonyl, 4-metyl-piperazinyl-carbonyl, 2-hydroxy-ethylamine-carbonyl, 2,6-dimethyl-4-morpholinyl-carbonyl, 4-morpholinyl-carbonyl, and $-NH_2$.

R5 may also represent a heteroaryl selected from the list consisting of pyridyl and imidazolyl, optionally substituted with a substituent selected from the list consisting of alkyl, halogen,

hydroxyl, cyano, nitro, haloalkyl, -O-R7, -S(O)$_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -(CH$_2$)$_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -(CH$_2$)$_p$-O-R7, -(CH$_2$)$_p$-N(R7)(R8), -NR7-C(O)R7, -NR7-S(O)$_n$-R7. In particular, said substituents are selected from the list consisting of fluoro, chloro, methyl, hydroxyl, cyano, nitro, -C(O)-O-R7, -C(O)-N(R7)(R8).

In a still further embodiment, R5 represents a heterocyclyl selected from the list consisting of piperidinyl, morpholinyl, piperazinyl and tetrafuranyl, optionally substituted with a substituent selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, haloalkyl, -O-R7, -S(O)$_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -(CH$_2$)$_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -(CH$_2$)$_p$-O-R7, -(CH$_2$)$_p$-N(R7)(R8), -NR7-C(O)R7, -NR7-S(O)$_n$-R7. In particular, said substituents are selected from the list consisting of of fluoro, chloro, hydroxyl, cyano, nitro, -C(O)-O-R7, -C(O)-N(R7)(R8), wherein R7 and R8 are as defined in claim 1.

In a still further embodiment, R7 and R8 independently represent hydrogen, alkyl, haloalkyl, hydroxyalkyl or phenyl.

In a still further embodiment, R9 and R10 independently represent hydrogen, alkyl, haloalkyl or hydroxyalkyl.

In a still further embodiment, R11 and R12 independently represent hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl or C_{1-6}hydoxyalkyl, such as hydrogen, methyl, ethyl, trifluoromethyl, hydroxymethyl or 2-hydroxyethyl.

In a still futher embodiment, R13 represents C_{1-6}alkyl, C_{1-6}haloalkyl or C_{1-6}hydroxyalkyl, such as methyl, ethyl, trifluoromethyl, hydroxymethyl or 2-hydroxyethyl.

In a still further embodiment, n is 2.

In a still further embodiment, p is 1.

Other embodiments of the invention can be seen from the claims.

Particular examples of the compounds of the present invention are

(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-methanesulfonyl-acrylonitrile;

(E)-2-(4-Chloro-benzenesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile;
(E)-2-(4-Chloro-benzenesulfonyl)-3-(4-hydroxy-3-nitro-phenyl)-acrylonitrile;
(E)-3-(4-Hydroxy-3-nitro-phenyl)-2-methanesulfonyl-acrylonitrile;
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(1-methyl-1H-imidazole-2-sulfonyl)-acrylonitrile;
(E/Z)-2-(4-Chloro-benzenesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-but-2-enenitrile;
(E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-benzoic acid;
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(4-nitro-benzenesulfonyl)-acrylonitrile;
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(4-trifluoromethoxy-benzenesulfonyl)-acrylonitrile;
(E)-3-(3-tert-Butyl-4-hydroxy-5-nitro-phenyl)-2-(4-chloro-benzenesulfonyl)-acrylonitrile;
(E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N,N-bis-(2-methoxy-ethyl)-benzamide;
(E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N,N-dimethyl-benzamide;
(E)-4-[3-Cyano-1-(3,5-di-tert!-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N,N-bis-(2-hydroxy-propyl)-benzamide;
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-[4-(4-methyl-piperazine-1-carbonyl)-benzenesulfonyl]-acrylonitrile;
(E)- 4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N-(2-hydroxy-ethyl)-benzamide;
(E)- 3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-[4-(2,6-dimethyl-morpholine-4-carbonyl)-benzenesulfonyl]-acrylonitrile;
(E)- 3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-[4-(morpholine-4-carbonyl)-benzenesulfonyl]-acrylonitrile;
(E)-2-(4-Amino-benzenesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile;
(E)-2-[2-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-ethenesulfonyl]-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile;
(E)-2-(4-Chloro-phenylmethanesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile;
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(propane-2-sulfonyl)-acrylonitrile.

Compounds according to formula I may comprise chiral carbon atoms or carbon-carbon double bonds which may give rise to stereo isomeric forms, e.g. enatiomers, diastereomers and geometric isomers. The present invention relates to all such isomers, either in pure form or as mixtures thereof. Pure isomeric forms may either be prepared from intermediates which are pure isomers themselves, by purification of a mixture of isomers after the synthesis, or by

a combination of the two methods. Purification of isomeric forms are well-known in the art, e.g. as described by Jaques in Enantiomers, Racemates and Resolution, Wiley, 1981.

The compounds of the present invention are believed to be particular well-suited for the treatment of obesity as such or preventing weight gain and for the treatment of diseases or disorders where obesity is involved in the etiology. In one embodiment, the invention thus provides a method of treating obesity, atherosclerosis, hypertension, type 2 diabetes, dyslipidemia, coronary heart disease, osteoarthritis, gallbladder diseases, and certain types of cancer, such as endometrial, breast, prostate and colon cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of one or more compound of the present invention to a patient need thereof. In particular, the invention provides a method for treatment of atherosclerosis, hypertension, type 2 diabetes, dyslipidemia, coronary heart disease, osteoarthritis, gallbladder diseases, and certain types of cancer, such as endometrial, breast, prostate and colon cancer, wherein the patient is obese.

Obesity drugs which regulate the appetite and reduce food intake often suffer from lack of long-term efficiency in terms of body weight loss because the body in response to the treatment lowers the rate of the metabolism. In contrast hereto, the compounds of the present invention increases the metabolism, and they are therefore believed to be particular suited for maintaining a weight loss.

The compounds of the present invention are also believed to be particular well-suited for the treatment of diseases or disorders where reactive oxygen species are involved in the etiology. In one embodiment, the invention thus provides a method of treating, and in particular preventing ageing and damages to the heart and neuronal tissue, the method comprising administering to a patient in need thereof a therapeutically effective amount of one or more compound of the present invention to a patient need thereof.

In the methods of the present invention, the compounds of the present invention may be administered alone or in combination with other therapeutically active compounds, either concomitantly or sequentially, and at any suitable ratios. Such further active compounds may be selected from antidiabetic agents, antihyperlipidemic agents, antiobesity agents, antihypertensive agents and agents for the treatment of complications resulting from or associated with diabetes.

Suitable antidiabetic agents include insulin, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S), which is incorporated herein by reference, as well as orally active hypoglycemic agents.

Suitable orally active hypoglycemic agents preferably include imidazolines, sulfonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, insulin sensitizers,

α-glucosidase inhibitors, agents acting on the ATP-dependent potassium channel of the pancreatic β-cells eg potassium channel openers such as those disclosed in WO 97/26265, WO 99/03861 and WO 00/37474 (Novo Nordisk A/S) which are incorporated herein by reference, potassium channel openers, such as ormitiglinide, potassium channel blockers such as nateglinide or BTS-67582, glucagon antagonists such as those disclosed in WO 99/01423 and WO 00/39088 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), all of which are incorporated herein by reference, GLP-1 agonists such as those disclosed in WO 00/42026 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, PTPase (protein tyrosine phosphatase) inhibitors, glucokinase activators, such as those described in WO 02/08209 to Hoffmann La Roche, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, GSK-3 (glycogen synthase kinase-3) inhibitors, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents, compounds lowering food intake, and PPAR (peroxisome proliferator-activated receptor) and RXR (retinoid X receptor) agonists such as ALRT-268, LG-1268 or LG-1069.

In one embodiment of the methods, the compound of the present invention may be administered in combination with insulin or insulin analogues.

In one embodiment, the compound of the present invnetion may be administered in combination with a sulphonylurea eg tolbutamide, chlorpropamide, tolazamide, glibenclamide, glipizide, glimepiride, glicazide or glyburide.

In one embodiment, the compound of the present invnetion may be administered in combination with a biguanide eg metformin.

In one embodiment of the methods of the present invention, the compound of the present invnetion may be administered in combination with a meglitinide eg repaglinide or senaglinide/nateglinide.

In one embodiment, the compound of the present invention may be administered in combination with a thiazolidinedione insulin sensitizer, e.g. troglitazone, ciglitazone, pioglitazone, rosiglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037 or T 174 or the compounds disclosed in WO 97/41097 (e.g. 5-[[4-[3-methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenylmethyl]thiazolidine-2,4-dione), WO 97/41119, WO 97/41120, WO 00/41121 and WO 98/45292, which are incorporated herein by reference.

In one embodiment, the compound of the present may be administered in combination with an insulin sensitizer e.g. such as GI 262570, YM-440, MCC-555, JTT-501, AR-H039242, KRP-297, GW-409544, CRE-16336, AR-H049020, LY510929, MBX-102, CLX-

0940, GW-501516 or the compounds disclosed in WO 99/19313 (NN622/DRF-2725), WO 00/50414, WO 00/63191, WO 00/63192, WO 00/63193 and WO 00/23425, WO 00/23415, WO 00/23451, WO 00/23445, WO 00/23417, WO 00/23416, WO 00/63153, WO 00/63196, WO 00/63209, WO 00/63190 and WO 00/63189, which are incorporated herein by reference.

In one embodiment, the compound of the present invention may be administered in combination with an α-glucosidase inhibitor eg voglibose, emiglitate, miglitol or acarbose.

In one embodiment, the compound of the present invnetion may be administered in combination with a glycogen phosphorylase inhibitor eg the compounds described in WO 97/09040.

In one embodiment, the compound of the present may be administered in combination with a glucokinase activator.

In one embodiment, the compound of the present invention may be administered in combination with an agent acting on the ATP-dependent potassium channel of the pancreatic β-cells eg tolbutamide, glibenclamide, glipizide, glicazide, BTS-67582 or repaglinide.

In one embodiment, the compound of the present invention may be administered in combination with nateglinide.

In one embodiment, the compound of the present invention may be administered in combination with an antihyperlipidemic agent or a antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In one embodiment, the compound of thenpresent may be administered in combination with more than one of the above-mentioned compounds e.g. in combination with metformin and a sulphonylurea such as glyburide; a sulphonylurea and acarbose; nateglinide and metformin; acarbose and metformin; a sulfonylurea, metformin and troglitazone; insulin and a sulfonylurea; insulin and metformin; insulin, metformin and a sulfonylurea; insulin and troglitazone; insulin and lovastatin; etc.

In one embodiment, the compound of the present invention may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC3 (melanocortin 3) agonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 adrenergic agonists such as CL-316243, AJ-9677, GW-0604, LY362884, LY377267 or AZ-40140, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK

(cholecystokinin) agonists, serotonin reuptake inhibitors (fluoxetine, seroxat or citalopram), norepinephrine reuptake inhibitors (e.g. sibutramine), 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth factors such as prolactin or placental lactogen, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA (dopamine) agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators, TR β agonists, adrenergic CNS stimulating agents, AGRP (agouti related protein) inhibitors, H3 histamine antagonists such as those disclosed in WO 00/42023, WO 00/63208 and WO 00/64884, which are incorporated herein by reference, exendin-4, GLP-1 agonists and ciliary neurotrophic factor. Further antiobesity agents are bupropion (antidepressant), topiramate (anticonvulsant), ecopipam (dopamine D1/D5 antagonist), naltrexone (opioid antagonist), and peptide YY_{3-36} (Batterham et al, Nature 418, 650-654 (2002)).

In one embodiment, the antiobesity agent is leptin.

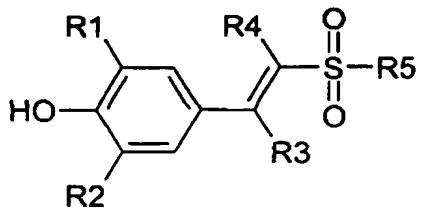
In one embodiment, the antiobesity agent is a lipase inhibitor eg orlistat.

In one embodiment, the antiobesity agent is an adrenergic CNS stimulating agent eg dexamphetamine, amphetamine, phentermine, mazindol phendimetrazine, diethylpropion, fenfluramine or dexfenfluramine.

In a further embodiment, the compounds of the present invention may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol; ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril; calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil; and α-blockers such as doxazosin, urapidil, prazosin and terazosin.

It should be understood that any suitable combination of the compounds according to the invention with diet and/or exercise, one or more of the above-mentioned compounds and optionally one or more other active substances are considered to be within the scope of the present invention.

The present invention also provides a method of treating obesity, type 2 diabetes, dyslipidemia, hypertension, gallbladder diaseases or preventing weight gain, which method comprises administering a therapeutically effective amount of a compound according to formula I



[I]

wherein each R1 and R2 independently represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, haloalkyl, alkoxy, alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6

-OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;

R3 represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, alkoxy ,alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6, -OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;

R4 represents nitro, cyano, halogen, haloalkyl, -C(O)R6, -C(O)OR6, -$C(O)N(R6)_2$ or –$S(O)_2$OR6, $S(O)_n$R6, $S(O)_2N(R6)_2$

-$P(O)(OR6)_2$ or –$B(OR6)_2$;

R6 represents hydrogen or alkyl, aryl or heteroaryl, all of which may be substituted with one or more substituent selected from amongst hydroxyl, halogen, nitro and cyano;

n represents 0, 1 or 2;

R5 represents alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, all of which are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, carboxyl, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -NR7-C(O)R7, NR7-$S(O)_n$R7,

-$(CH_2)_p$-N(R7)(R8) and phenyl, said phenyl being optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, nitro, O-R13, -$S(O)_n$R11, -O-C(O)R11, -C(O)-O-R11, -C(O)-R11 -C(O)-N(R11)(R12), -N(R11)(R12), -$(CH_2)_p$-N(R11)-C(O)-R12, -B(OR11)(OR12), -$(CH_2)_p$-O-R11, -$(CH_2)_p$-N(R11)(R12) ;

R7 and R8 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, dialkylether, cycloalkyl, heterocyclyl or phenyl, wherein said phenyl and heterocyclyl are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyl, hydroxyalkyl, cyano, nitro, -N(R9)(R10) and –$(CH_2)_p$-N(R9)(R10);

R9 and R10 independently represent hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl or cycloalkyl;

or R4 and R5 together with the atoms to which they are attached constitute a 5, 6, 7 or 8 membered ring, which may be saturated, either partly or fully or unsaturated, and wherein said ring is optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano and nitro;

each R11 and R12 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl or phenyl;

R13 represents haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalyl;

p represents 0, 1 or 2;

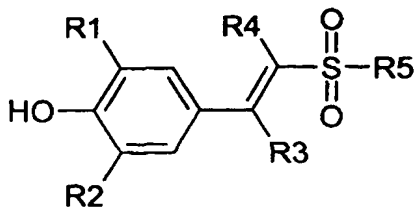
and pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof.to a patient in need thereof, optionally in combination with other therapeutically active compounds as mentioned above, wherein said other compound is being administered concomitantly or sequentially. In particular, the said method can be used to treat type 2 diabetes, dyslipidemia, hypertension and gallbladder diseases wherein the patient is obese.

The present invention also provides pharmaceutical compositions comprising as an active ingredient, at least one compound of the present invention, preferably in a therapeutically effective amount, suitable for any of the methods according to the present invention together with one or more pharmaceutically acceptable carriers or excipients. Said pharmaceutical compositions may also comprise any of the further active compounds as indicated above

The pharmaceutical composition is preferably in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of a compound suitable for any of the methods described above.

In a further embodiment, the present invention relates to the use of a compound of the present invention in the manufacture of a medicament for the treatment of obesity or diseases or disorders where obesity is involved in the etiology, such as atherosclerosis, hypertension, type 2 diabetes, dyslipidemia, coronary heart disease, osteoarthritis, gallbladder diseases, and certain types of cancer, such as endometrial, breast, prostate and colon cancer, or diseases or disorders where reactive oxygen species are involved in the etiology, such as ageing and damages to the heart and neuronal tissue or for preventing weight gain.

In a still further embodiment, the invention relates to the use of a compound according to formula I



[I]

wherein each R1 and R2 independently represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, haloalkyl, alkoxy, alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6
-OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;
R3 represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, alkoxy ,alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6, -OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;
R4 represents nitro, cyano, halogen, haloalkyl, -C(O)R6, -C(O)OR6, -$C(O)N(R6)_2$ or –$S(O)_2$OR6, $S(O)_n$R6, $S(O)_2N(R6)_2$
-$P(O)(OR6)_2$ or –$B(OR6)_2$;
R6 represents hydrogen, alkyl, aryl or heteroaryl, all of which may be substituted with one or more substituent selected from amongst hydroxyl, halogen, nitro and cyano and hydrogen;
n represents 0, 1 or 2;
R5 represents alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, all of which are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, carboxyl, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -NR7-C(O)R7, NR7-$S(O)_n$R7,
-$(CH_2)_p$-N(R7)(R8) and phenyl, said phenyl being optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, nitro, O-R13, -$S(O)_n$R11, -O-C(O)R11, -C(O)-O-R11, -C(O)-R11 -C(O)-N(R11)(R12), -N(R11)(R12), -$(CH_2)_p$-N(R11)-C(O)-R12, -B(OR11)(OR12), -$(CH_2)_p$-O-R11, -$(CH_2)_p$-N(R11)(R12) ;
R7 and R8 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, dialkylether, cycloalkyl, heterocyclyl or phenyl, wherein said phenyl and heterocyclyl are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyl, hydroxyalkyl, cyano, nitro, -N(R9)(R10) and –$(CH_2)_p$-N(R9)(R10);
R9 and R10 independently represent hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl or cycloalkyl;

or R4 and R5 together with the atoms to which they are attached constitute a 5, 6, 7 or 8 membered ring, which may be saturated, either partly or fully or unsaturated, and wherein said ring is optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano and nitro;

each R11 and R12 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl or phenyl;

R13 represents haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalyl;

p represents 0, 1 or 2;

and pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof in the manufacture of a medicament for the treatment of obesity, type 2 diabetes, dyslipidemia, hypertension, gallbladder diseases or for preventing weight gain, optionally in combination with other therapeutically active compounds as mentioned above.

PHARMACEUTICAL COMPOSITIONS

The compounds for methods according to the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as hard or soft capsules, tablets, troches, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, aqueous or oily suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds for use according to the present invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. Examples are an acid addition salt of a compound having the utility of a free base and a base addition salt of a compound having the utility of a free acid. The term "pharmaceutically acceptable salts" refers to non-toxic salts of the compounds for use according to the present invention which salts are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. When a compound for use according to the present invention contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of the compound with a chemical equivalent of a pharmaceutically acceptable acid. When a compound for use according to the present invention, contains a free acid such salts are prepared in a conventional manner by treating a solution or suspension of the compound with a chemical equivalent of a pharmaceutically acceptable base. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound

in combination with a suitable cation such as sodium or ammonium ion. Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of the invention and these form a further aspect of the invention.

For parenteral administration, solutions of the compounds for use according to the present invention in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the compounds for use according to the present invention and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

Compositions intended for oral use may be prepared according to any known method, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically-acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example, starch, gelatine or acacia; and lubricating agents, for ex-

ample magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,356,108; 4,166,452; and 4,265,874, incorporated herein by reference, to form osmotic therapeutic tablets for controlled release.

Formulations for oral use may also be presented as hard gelatine capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatine capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions may contain the compound for use according to the present invention in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide such as lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as a liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active compound in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Addi-

tional excipients, for example, sweetening, flavouring, and colouring agents may also be present.

The pharmaceutical compositions comprising compounds for use according to the present invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example a liquid paraffin, or a mixture thereof. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known methods using suitable dispersing or wetting agents and suspending agents described above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conveniently employed as solvent or suspending medium. For this purpose, any bland fixed oil may be employed using synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compositions may also be in the form of suppositories for rectal administration of the compounds of the invention. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will thus melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols, for example.

For topical use, creams, ointments, jellies, solutions of suspensions, etc., containing the compounds of the invention are contemplated. For the purpose of this application, topical applications shall include mouth washes and gargles.

The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes may be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

In addition, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are also encompassed within the scope of the invention.

Thus, in a further embodiment, there is provided a pharmaceutical composition comprising a compound for use according to the present invention, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet that may be prepared by conventional tabletting techniques may contain:

Core:		
Example 2 (as free compound or salt thereof)	5.0 mg	
Lactosum Ph. Eur.		67.8 mg
Cellulose, microcryst. (Avicel)		31.4 mg
Amberlite®IRP88*		1.0 mg
Magnesii stearas Ph. Eur.		q.s.
Coating:		
Hydroxypropyl methylcellulose	approx.	9 mg
Mywacett 9-40 T**	approx.	0.9 mg

* Polacrillin potassium NF, tablet disintegrant, Rohm and Haas.

** Acylated monoglyceride used as plasticizer for film coating.

If desired, the pharmaceutical composition comprising a compound for use according to the present invention may comprise a compound for use according to the present invention in combination with further active substances such as those described in the foregoing.

The present invention also provides methods for the preparation of compounds for use according to the present invention. The compounds can be prepared readily according to the following general procedures (in which all variables are as defined before, unless so

specified) using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail.

Examples:

HPLC-MS (Method A)

The following instrumentation is used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- Hewlett Packard series 1100 G1315A DAD diode array detector
- Hewlett Packard series 1100 MSD
- Sedere 75 Evaporative Light Scattering detector

The instrument is controlled by HP Chemstation software.

The HPLC pump is connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: 0.01% TFA in acetonitrile

The analysis is performed at 40°C by injecting an appropriate volume of the sample (preferably 1 µl) onto the column which is eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings used are giving in the following table.

Column: Waters Xterra MS C-18 X 3 mm id 5 □m

Gradient: 5% - 100% acetonitrile linear during 7.5 min at 1.5ml/min

Detection: 210 nm (analogue output from DAD (diode array detector))

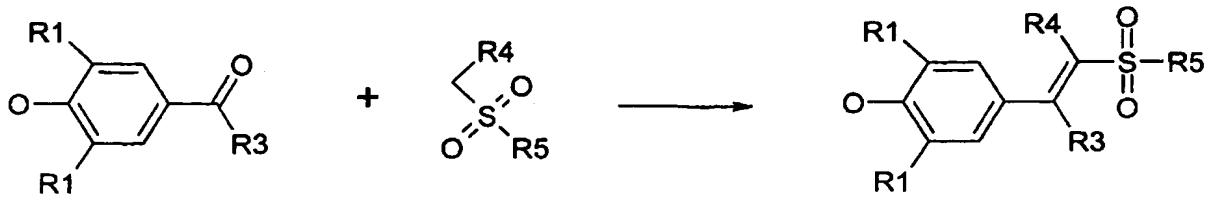
ELS (analogue output from ELS)

MS ionisation mode API-ES

Scan 100-1000 amu step 0.1 amu

After the DAD the flow is divided yielding approx 1 ml/min to the ELS and 0.5 ml/min to the MS.

General procedure A:



To a solution of the appropriate carbonylcompound (1 mmole) in ethanol 4 ml, the appropriate sulfonylcompound (1mmole) and a catalytic amount of piperidine (0.1 mmole) was added. The reaction mixture was heated at reflux for 12 hours. The products were isolated either by,

Step A: cooling filtration and crystallisation

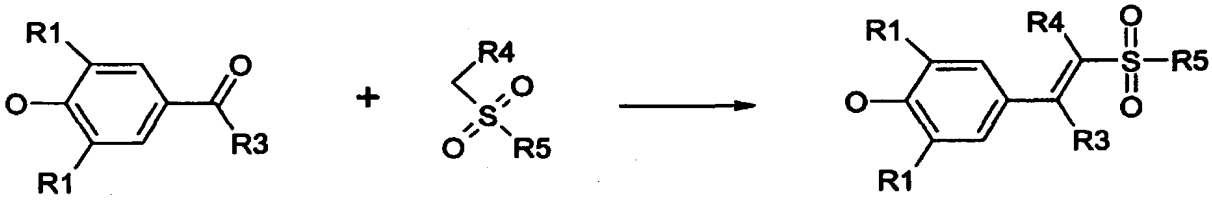
or

Step B: cooling, separation of the compound with water, and crystallisation with an organic solvent

or

Step C: Aquae's work up followed by column chromatography

General procedure B:



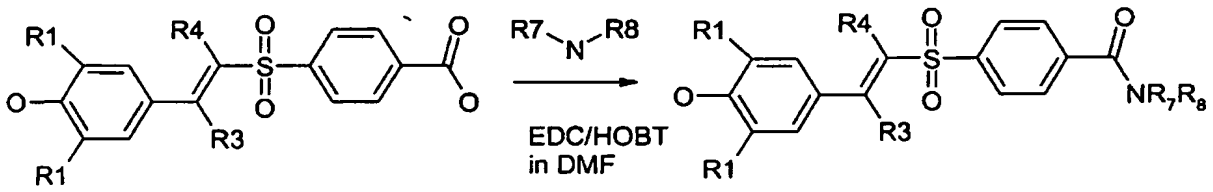
To a solution of the appropriate carbonylcompound (1 mmole) in toluene 10 ml, the appropriate sulfonylcompound (1 mmole) and ammonium acetate (1 mmole) was added. The reaction mixture was heated at reflux water for 12 hours with continuous separation of water. The products were isolated either by

Step A: Aquae's work up followed by column chromatography

or

Step C: Aqua's work up followed by crystallisation.

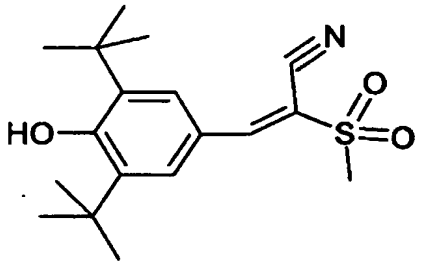
General procedure C



To a solution of compound of the general formula in DMF, 1.5 molar equivalent of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide and 1 molar equivalent of hydroxybenzotriazole are added. The reaction mixture is stirred at room temperature for 0.5 hour, whereupon a compound of the general formula and triethylamine 1 equivalent are added. The reaction mixture is stirred at room temperature overnight. The compounds synthesised by this general procedure is purified by aqueous work-up followed by crystallisation from an organic solvent.

Example 1 (General procedure (A))

(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-methanesulfonyl-acrylonitrile

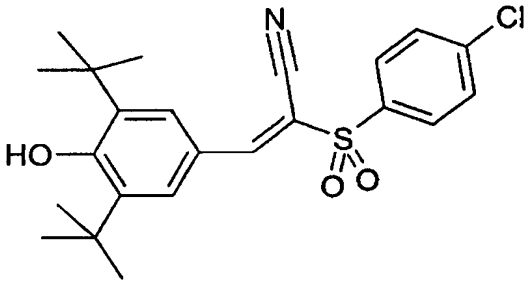


Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and methanesulfonylacetonitrile in 35 % yield.

^{1}H NMR ($CDCl_3$): δ 1.47 (s, 18 H) 3.18 (s, 3 H) 6.03 (s, 1 H) 7.86 (s, 2 H) 8.04 (s, 1 H); HPLC-MS (Method A): *m/z* = 358 (M+Na); R_t = 4.79 min.

Example 2 (General procedure (A))

(E)-2-(4-Chloro-benzenesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile

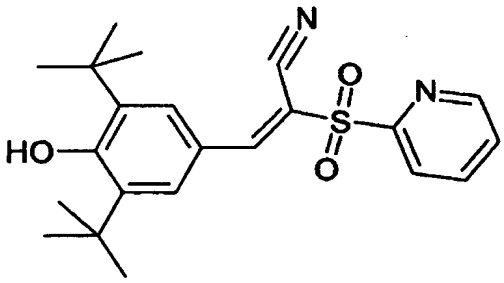


Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and 4-chlorophenylsulfonylacetonitrile in 72 % yield

^{1}H NMR ($CDCl_3$): δ 1.45 (s, 18 H) 6.01 (s, 1 H) 7.56 (d, *J*=8.59 Hz, 2 H) 7.83 (s, 2 H) 7.94 (d, *J*=8.59 Hz, 2 H) 8.12 (s, 1 H); HPLC-MS (Method A): *m/z* = 432 (M+1); R_t = 4.88 min.

Example 3 (General procedure (A))

(E)-3-(3,5-Di-tert!-butyl-4-hydroxy-phenyl)-2-(pyridine-2-sulfonyl)-acrylonitrile

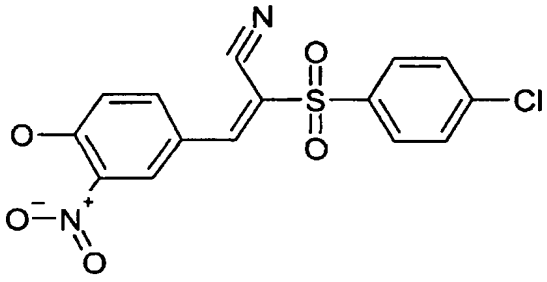


Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and pyridine-2-sulfonylacetonitrile in 88 % yield

^{1}H NMR (DMSO-d_6): δ ppm 1.38 (m, 18 H) 7.81 (m, 1 H) 8.00 (s, 2 H) 8.23 (m, 2 H) 8.41 (s, 1 H) 8.51 (m, 1 H) 8.81 (m, J=4.52 Hz, 1 H); HPLC-MS (Method A): m/z = 400 (M+1); R_t = 4.9 min.

Example 4 (General procedure (A))

(E)-2-(4-Chloro-benzenesulfonyl)-3-(4-hydroxy-3-nitro-phenyl)-acrylonitrile

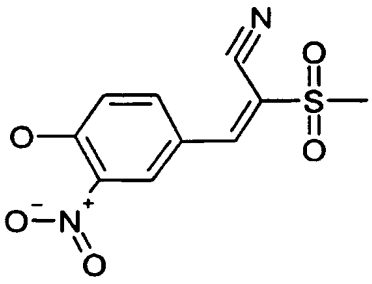


Step A: The title compound was prepared from 3-tert-butyl-5-nitro-4-hydroxybenzaldehyde and pyridine-2-sulfonylacetonitrile in 67 % yield

^{1}H NMR (DMSO-d_6): δ ppm 7.30 (d, J=9.10 Hz, 1 H) 7.83 (d, J=8.59 Hz, 2 H) 8.02 (d, J=8.59 Hz, 2 H) 8.21 (dd, 1 H) 8.55 (s, 1 H) 8.66 (d, J=2.02 Hz, 1 H); HPLC-MS (Method A): m/z = 365 (M+1); R_t = 3.88 min.

Example 5 (General procedure (A))

(E)-3-(4-Hydroxy-3-nitro-phenyl)-2-methanesulfonyl-acrylonitrile

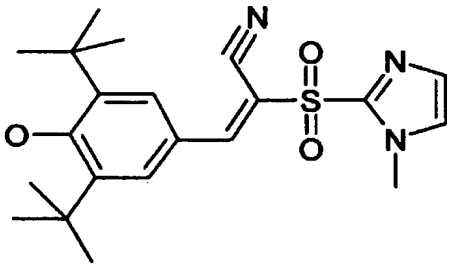


Step A: The title compound was prepared from 3-tert-butyl-5-nitro-4-hydroxybenzaldehyde and methanesulfonylacetonitrile in 57 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 3.34 (m, 3 H) 7.28 (d, J=9.10 Hz, 1 H) 8.20 (dd, J=9.10, 2.53 Hz, 1 H) 8.27 (s, 1 H) 8.64 (d, J=2.02 Hz, 1 H); HPLC-MS (Method A): m/z = 269 (M+1); R_t = 2.67 min.

Example 6 (General procedure (A))

(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(1-methyl-1H-imidazole-2-sulfonyl)-acrylonitrile

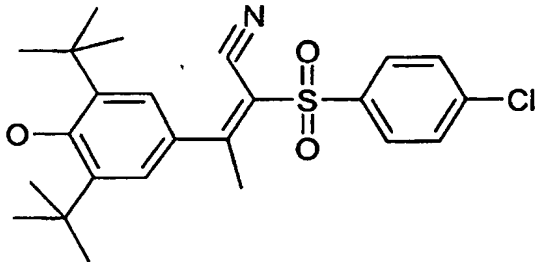


Step C: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and 1-methylimidazol-2-ylsulfonylacetonitrile in 8 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 1.29 (s, 18 H) 3.95 (m, 3 H) 7.05 (s, 1 H) 7.44 (s, 1 H) 7.52 (s, 1 H) 7.63 (s, 2 H) 8.22 (s, 1 H); HPLC-MS (Method A): m/z = 421 (M+1); R_t =4.6 min.

Example 7 (General procedure (B))

(E/Z)-2-(4-Chloro-benzenesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-but-2-enenitrile

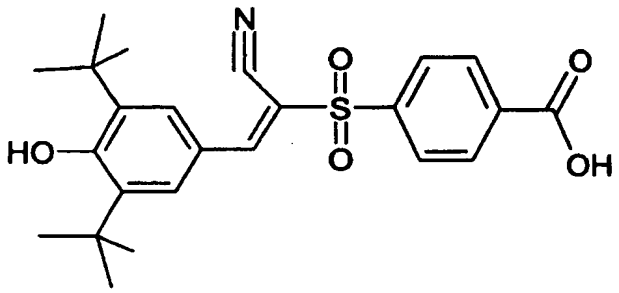


Step A: The title compound was prepared from 3-tert-butyl-5-nitro-4-hydroxyacetophenone and pyridine-2-sulfonylacetonitrile in 2 % yield.

^{1}H NMR ($CDCl_3$): (E) δ ppm 1.43 (s, 18 H) 2.69 (s, 3 H) 5.66 (m, 1 H) 7.33 (s, 2 H) 7.59 (d, J=9.04 Hz, 2 H) 8.00 (d, J=8.67 Hz, 2 H); ^{1}H NMR ($CDCl_3$): (Z) δ ppm 1.41 (s, 18 H) 2.51 (m, 3 H) 5.55 (s, 1 H) 6.92 (s, 2 H) 7.26 (d, 2 H) 7.39 (d, 2 H); HPLC-MS (Method A): m/z = 468 (M+23); R_t = 5.6 min.

Example 8 (General procedure (A))

(E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-benzoic acid

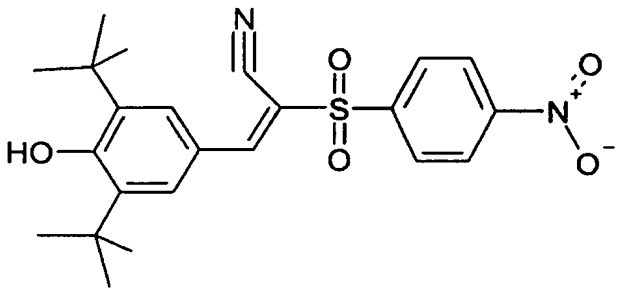


Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and 4-carboxyphenylsulfonylacetonitrile in 90 % yield

^{1}H NMR (DMSO-d_6): δ ppm 1.39 (s, 18 H) 7.97 (s, 2 H) 8.11 (d, J=8.08 Hz, 2 H) 8.22 (d, J=8.08 Hz, 2 H) 8.48 (s, 1 H) 8.54 (m, 1 H) 13.65 (m, 1 H); HPLC-MS (Method A): m/z = 442 (M+1); R_t = # min.

Example 9 (General procedure (A))

(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(4-nitro-benzenesulfonyl)-acrylonitrile

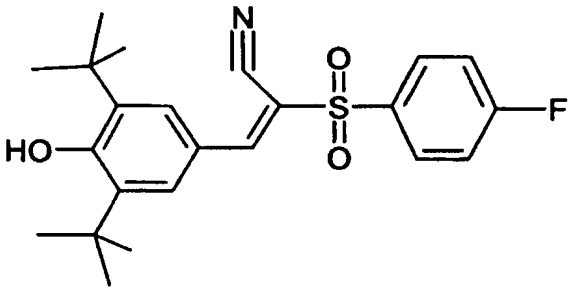


Step C: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and 4-nitrophenylsulfonylacetonitrile in 27 % yield

^{1}H NMR (DMSO-d_6): δ ppm 1.39 (s, 18 H) 7.69 (s, 1 H) 7.98 (s, 2 H) 8.27 (d, J=8.59 Hz, 2 H) 8.49 (d, 2 H) 8.53 (s, 1 H); HPLC-MS (Method A): m/z = 443 (M+1); R_t = # min.

Example 10 (General procedure (A))

(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(4-fluoro-benzenesulfonyl)-acrylonitrile

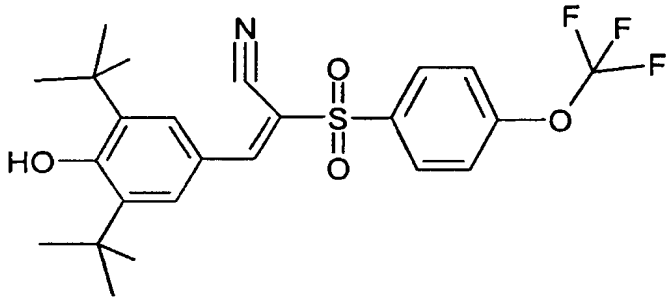


Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and 4-fluoronitrophenylsulfonylacetonitrile in 37 % yield

^{1}H NMR (DMSO-d_6): δ ppm 1.39 (m, 18 H) 7.58 (dd, J=8.84 Hz, 2 H) 7.95 (s, 2 H) 8.08 (dd, J=9.10, 5.05 Hz, 2 H) 8.44 (s, 1 H) 8.46 (s, 1 H); HPLC-MS (Method A): m/z = 416 (M+1); R_t = # min.

Example 11 (General procedure (A))

(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(4-trifluoromethoxy-benzenesulfonyl)-acrylonitrile

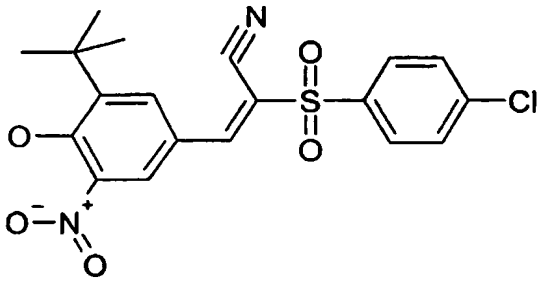


Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and 4-trifluoromethoxyphenylsulfonylacetonitrile in 69 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 1.41 (m, 18 H) 7.72 (d, J=8.08 Hz, 2 H) 7.96 (s, 2 H) 8.14 (d, J=9.10 Hz, 2 H) 8.46 (s, 1 H) 8.50 (s, 1 H); HPLC-MS (Method #): m/z = 482 (M+1); R_t = # min.

Example 12

(E)-3-(3-tert-Butyl-4-hydroxy-5-nitro-phenyl)-2-(4-chloro-benzenesulfonyl)-acrylonitrile

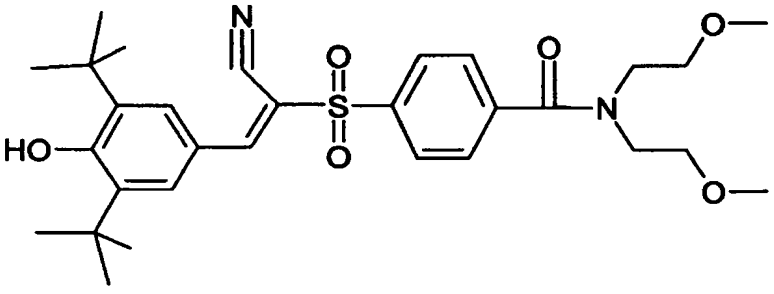


To a suspension of (E)-2-(4-Chloro-benzenesulfonyl)-3-(4-hydroxy-3-nitro-phenyl)-acrylonitrile (250 mg, 0.58 mmole) in acetic acid, nitric acid (72 mg, 1.16 mmole) was added. The reaction mixture was stirred at room temperature for 1 hour. Water was added to the reaction mixture and the separated crystal were filtered. The title compound was purified by column chromatography with dichloromethane as eluent. Yield 35 mg, 14%.

^{1}H NMR ($CDCl_3$): δ ppm 1.46 (s, 9 H) 7.60 (d, J=8.67 Hz, 2 H) 7.96 (d, J=8.67 Hz, 2 H) 8.15 (s, 1 H) 8.33 (d, J=1.88 Hz, 1 H) 8.52 (d, J=2.26 Hz, 1 H) 12.03 (s, 1 H); HPLC-MS (Method A): m/z = 444 (M+Na); R_t = 5.4 min.

Example 13 (General procedure (C))

(E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N,N-bis-(2-methoxy-ethyl)-benzamide

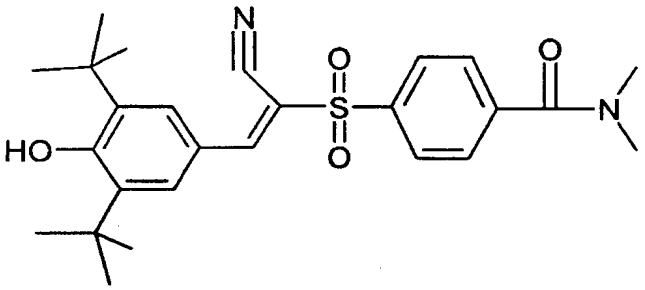


Step A: the title compound was prepared from (E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-benzoic acid and bis(2-methoxyethyl)amine in 62 % yield.

^{1}H NMR ($CDCl_3$): δ ppm 1.46 (s, 18 H) 3.27 (s, 3 H) 3.38 (s, 3 H) 3.46 (m, 4 H) 3.67 (m, J=4.55 Hz, 2 H) 3.75 (m, J=4.55 Hz, 2 H) 6.02 (s, 1 H) 7.64 (d, J=8.59 Hz, 2 H) 7.84 (s, 2 H) 8.03 (d, J=8.59 Hz, 2 H) 8.13 (s, 1 H); HPLC-MS (Method A): m/z = 557 (M+1); R_t = 4.92 min.

Example 14 (General procedure (C))

(E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N,N-dimethyl-benzamide

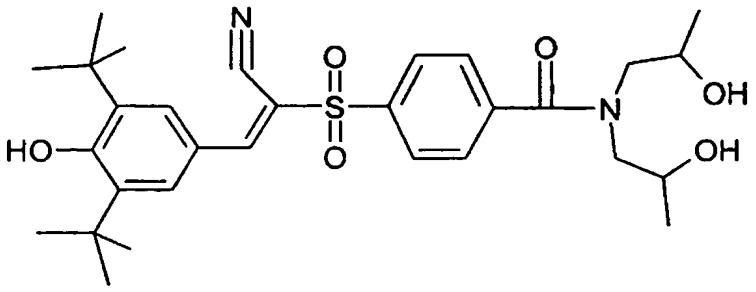


The title compound was prepared from (E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-benzoic acid dimethylamine in 90 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 2.86 (s, 3 H) 7.72 (d, J=8.59 Hz, 2 H) 7.95 (s, 2 H) 8.03 (d, J=8.08 Hz, 2 H) 8.44 (s, 1 H) 8.47 (s, 1 H); HPLC-MS (Method A): m/z = 469 (M+1); R_t = 4.99 min.

Example 15 (General procedure (C))

(E)-4-[3-Cyano-1-(3,5-di-tert!-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N,N-bis-(2-hydroxy-propyl)-benzamide.

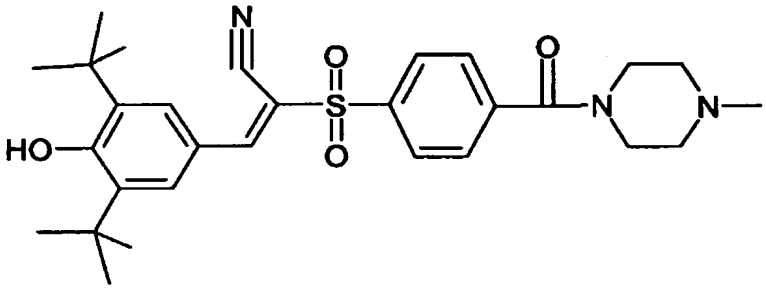


The title compound was prepared from (E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-benzoic acid diisopropanolamine in 32 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 0.83 (d, 4 H) 1.10 (d, 3 H) 1.38 (m, 18 H) 3.14 (m, 2 H) 3.43 (m, 2 H) 3.76 (m, 1 H) 4.00 (m, 1 H) 4.91 (m, 2 H) 7.71 (d, J=8.59 Hz, 2 H) 7.96 (s, 2 H) 8.03 (d, J=7.07 Hz, 2 H) 8.46 (s, 2 H); HPLC-MS (Method A): m/z = 557(M+1); R_t = 4.71 min.

Example 16 (General procedure (C))

(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-[4-(4-methyl-piperazine-1-carbonyl)-benzenesulfonyl]-acrylonitrile.

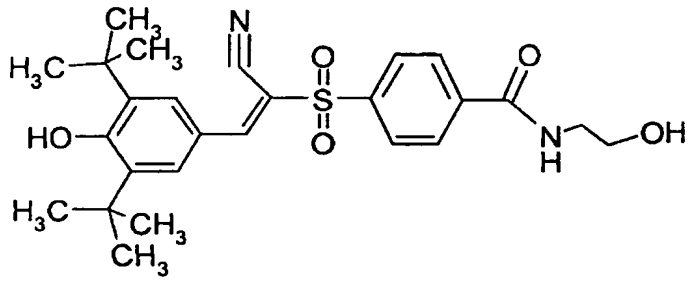


Step A: The title compound was prepared from (E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-benzoic acid N-methylpiperazine in 38 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 1.39 (s, 18 H) 2.81 (s, 3 H) 3.53 (m, 8 H) 7.78 (d, J=8.59 Hz, 2 H) 7.97 (s, 2 H) 8.10 (d, J=8.59 Hz, 2 H) 8.47 (s, 1 H); HPLC-MS (Method A): m/z = 534 (M+1); R_t = 3.85 min.

Example 17 (General procedure (C))

(E)- 4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N-(2-hydroxy-ethyl)-benzamide.

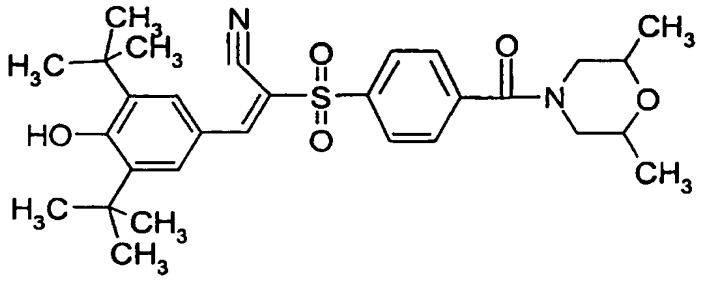


Step A: The title compound was prepared from (E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-benzoic acid and ethanolamine in 28 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 1.38 (s, 18 H) 3.29 (m, 2 H) 3.51 (t, J=6.06 Hz, 2 H) 4.77 (m, 1 H) 7.93 (s, 2 H) 8.07 (d, J=8.59 Hz, 2 H) 8.11 (d, 2 H) 8.42 (s, 1 H) 8.49 (m, 1 H) 8.75 (t, J=5.81 Hz, 1 H); HPLC-MS (Method A): m/z = 486 (M+1); R_t = 4.23 min.

Example 18 (General procedure (A))

(E)- 3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-[4-(2,6-dimethyl-morpholine-4-carbonyl)-benzenesulfonyl]-acrylonitrile.

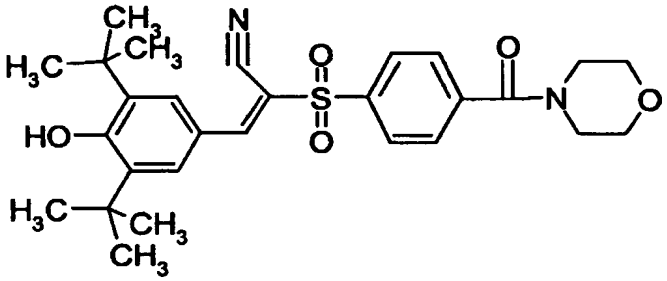


Step A: The title compound was prepared from (E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-benzoic acid and 2,6-dimethylmorpholine in 65 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 0.97 (d, J=5.05 Hz, 3 H) 1.15 (d, J=5.05 Hz, 3 H) 1.38 (s, 18 H) 2.82 (t, 1 H) 3.32 (m, J=13.64 Hz, 2 H) 3.55 (m, 2 H) 4.37 (d, J=12.13 Hz, 1 H) 7.72 (d, J=8.08 Hz, 2 H) 7.96 (s, 2 H) 8.05 (d, J=8.08 Hz, 2 H) 8.46 (s, 1 H) 8.48 (s, 1 H); HPLC-MS (Method A): m/z = 538 (M+1); R_t = 5.05 min.

Example 19 (General procedure (C))

(E)- 3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-[4-(morpholine-4-carbonyl)-benzenesulfonyl]-acrylonitrile.

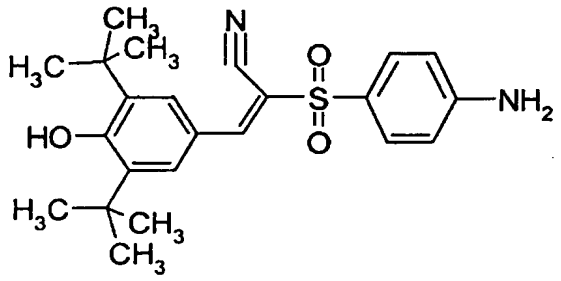


Step A: The title compound was prepared from (E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-benzoic acid and morpholine in 83 % yield.

^{1}H NMR (DMSO-d_6): δ ppm 1.39 (s, 18 H) 3.27 (s, 2 H) 3.53 (s, 2 H) 3.65 (m, 4 H) 7.74 (d, J=8.59 Hz, 2 H) 7.97 (s, 2 H) 8.06 (d, J=8.08 Hz, 2 H) 8.47 (s, 1 H) 8.49 (m, 1 H); HPLC-MS (Method #): m/z = 511 (M+1); R_t = 4.70 min.

Example 20 (General procedure (A))

(E)-2-(4-Amino-benzenesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile

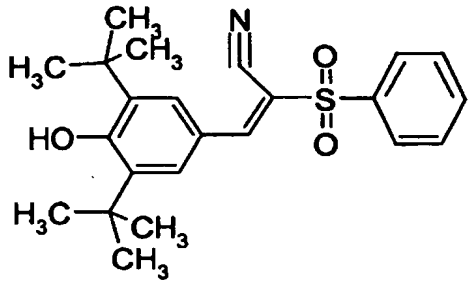


Step C: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and 4-aminophenylsulfonylacetonitrile in 55 % yield.

^{1}H NMR ($CDCl_3$): δ ppm 1.45 (s, 18 H) 4.28 (s, 2 H) 5.92 (s, 1 H) 6.71 (d, J=8.59 Hz, 2 H) 7.74 (d, J=9.10 Hz, 2 H) 7.81 (s, 2 H) 8.07 (s, 1 H); HPLC-MS (Method A): m/z = 413 (M+1); R_t = 4.80 min.

Example 21 (General procedure (A))

(E)-2-Benzenesulfonyl-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile

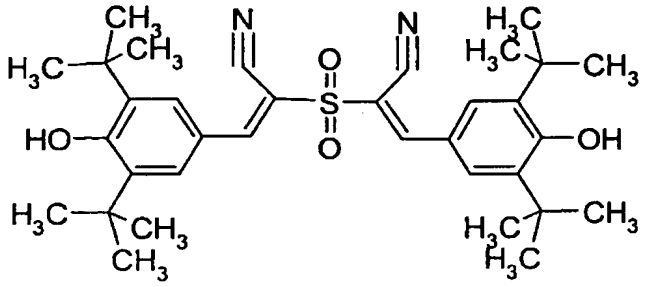


Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and phenylsulfonylacetonitrile in 61 % yield

^{1}H NMR (DMSO-d_6): δ ppm 1.39 (s, 18 H) 7.76 (m, 3 H) 7.95 (s, 2 H) 8.00 (d, J=7.16 Hz, 2 H) 8.44 (s, 2 H); HPLC-MS (Method #): m/z = 399 (M+1); R_t = 5.5 min.

Example 22 (General procedure (A))

(E)-2-[2-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-ethenesulfonyl]-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile

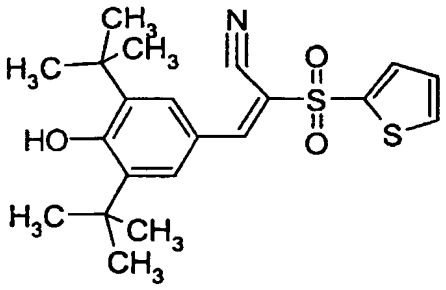


Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and sulfonyldiacetonitrile in 14 % yield

^{1}H NMR (DMSO-d_6): δ ppm 1.41 (s, 36 H) 8.03 (s, 4 H) 8.38 (s, 2 H) 8.58 (s, 2 H); HPLC-MS (Method #): m/z = 600 (M+23); R_t = 6.6 min.

Example 23 (General procedure (A))

(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(thiophene-2-sulfonyl)-acrylonitrile

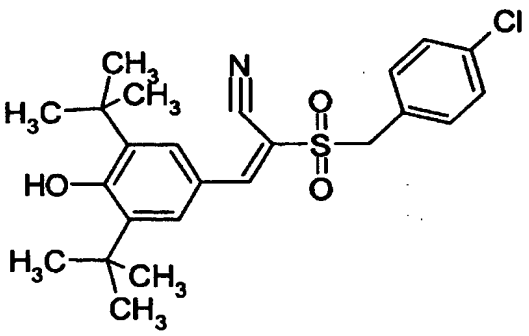


Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and thiophene-2-sulfonylacetonitrile in 66 % yield

^{1}H NMR (DMSO-d_6): δ 1.39 (s, 18 H) 7.34 (dd, J=4.52 Hz, 1 H) 7.91 (d, J=3.77 Hz, 1 H) 7.96 (s, 2 H) 8.23 (d, J=4.90 Hz, 1 H) 8.42 (s, 1 H) 8.46 (m, 1 H); HPLC-MS (Method #): m/z = 404 (M+23); R_t = 5.3 min.

Example 24 (General procedure (A))

(E)-2-(4-Chloro-phenylmethanesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile

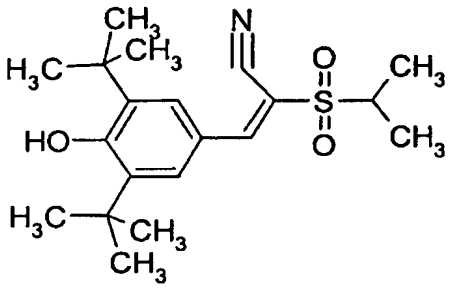


Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and 4-chlorobenzylsulfonylacetonitrile in 17 % yield

^{1}H NMR (DMSO-d_6): δ ppm 1.39 (s, 18 H) 4.82 (s, 2 H) 7.42 (d, J=8.67 Hz, 2 H) 7.48 (d, 2 H) 7.83 (s, 2 H) 7.92 (s, 1 H) 8.43 (s, 1 H); HPLC-MS (Method A): m/z = 469 (M+1); R_t = 5.4 min.

Example 25 (General procedure (A))

(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(propane-2-sulfonyl)-acrylonitrile



Step A: The title compound was prepared from 3,5-di-tert-butyl-4-hydroxybenzaldehyde and propane-2-sulphonylacetonitrile in 34 % yield

^{1}H NMR (DMSO-d_6): δ ppm 1.32 (d, J=6.78 Hz, 6 H) 1.41 (s, 18 H) 3.56 (m, 1 H) 7.98 (s, 2 H) 8.16 (s, 1 H) 8.41 (s, 1 H); HPLC-MS (Method A): m/z = 464 (M+1); R_t = 5.0 min.

PHARMACOLOGICAL METHODS

Assay (I): Glucose utilisation in a human epithelia cell line (FSK-4 cells)

Assay description:

The assay measures indirectly the activity of the respiratory chain in FSK-4 cells by using D-(6-^{3}H(N))-glucose. The ^{3}H-proton will first be released in the TCA cyclus and transported to the respiratory chain where it will be incorporated into water. The water is thereafter

separated from the D-(6-^{3}H(N))-glucose by evaporation. Finally, the radioactivity in the water is determined using a Topcounter.

Method:

FSK-4 cells obtained from ATCC (Maryland, USA), are cultured in growth medium (McCoy's medium with the following addition 100 units/ml penicillin and streptomycin and 10 % FCS (fetal calf serum)) at 37°C and 5% CO_2. All media are obtained by Gibco (Life Technologies, Maryland, USA) where not otherwise mentioned.

At day zero the cells are harvested using trypsin-EDTA and washed in assay medium (MEM medium with the following addition 1x non-essential amino acids (M7145, 2 mM glutamin, 100 units/ml pencillin and streptomycin, 0.0075% sodium bicarbonate, 1 mM sodium pyrovate and 2 % horse serum) using centrifugation. The cells are plated into single StripPlates wells (Corning B.V.Life Sciences, The Netherlands) that are placed into 24-well plates (Corning B.V.Life Sciences, The Netherlands) with a concentration of $1{,}5x10^4$ cells/100 μl assay medium/well. The cells are then incubated at 37°C and 5% CO_2 overnight.

The next day the compounds to be tested are diluted to different concentrations in DMSO (Sigma, Missouri, USA) to 100 times final concentration. They are then diluted to a final concentration in assay medium containing 10 μCi/ml D-(6-^{3}H(N))-glucose (PerkinElmer Life Sciences Inc.,Boston, USA). The medium is removed from the cells and 200 μl of the compound dilutions are added in duplicates. The cells are then incubated for another 24 hours at 37°C and 5% CO_2. Finally the cells are lysed by adding 50 µl 10% TCA (trichloroacetate). 300 µl of sterile water is then added to the 24-wells that surrounds the StripPlate wells. The plate is sealed with Top-seal-tape (Packard, PerkinElmer Life Sciences Inc.,Boston, USA) and the plate is incubated in a heating cupboard at 50°C to equilibrium the radioactive water formed in the respiratory chain into the water in the 24-well plate by evaporate. The plates incubate for 8 hours where the heating cupboard is turned off. The top seal is removed when the samples have reached room temperature. One ml scintillation liquid (Packard Microscient, PerkinElmer Life Sciences Inc.,Boston, USA) is added to all the samples and the radioactivity is determined using a Topcounter (Packard, PerkinElmer Life Sciences Inc.,Boston, USA). Non-specific activity is determined by evaporating 200 μl of the dilution medium containing the D-(6-^{3}H(N))-glucose into 300 μl sterile water, and total radioactivity is determined by counting 5 μl assay medium with 10 μCi/ml D-(6-^{3}H(N))-glucose.

Calculations

The half maximal concentration (EC_{50}) and maximal efficacy (E_{max}) are calculated using the Hill equation in GraphPad Prism 3.0 (GraphPad software, Inc.). In studies where the linear

slope is determined the following concentration of the compound is used; 5x, 3x, 2x, 1,5x, 1,25x, 1x, 0.85x, 0.7x, 0.5x, 0.3x, 0.2x and 0x EC_{50}. From the percentage increase in glucose utilisation the linear slope is calculated using the Michaelis-Menten equation.

Assay (II):The effect of chemical uncouplers on mitochondrial respiration using isolated mitochondria.

This assay is used to investigate if the increase in glucose utilisation caused by the test compounds observed in the glucose utilisation assay is due to an increase in the respiration of the mitochondria. This is done by measuring oxygen consumption in isolated rat liver mitochondria.

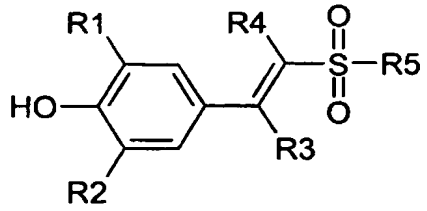
A Clark oxygen electrode is used to determine the oxygen consumption. The isolated mitochondria are added to assay medium (D-Mannitol 220mM, MagnesiumCloride 5mM, HEPES 2 mM and PotassiumPhosphate 5mM, pH = 7,4) containing rotenone (an inhibitor of clomplex 1) and oligomyocin (an inhibitor of the ATP-synthase) and the rate of oxygen consumptions is measured, when stabilized nutrient (e.g. succinate) is added and an increase in the rate of oxygen consumption is measured. When the rate of oxygen consumption again has stabilized the test compound is added and the oxygen consumption is measured. If the test compound stimulates the rate of oxygen consumption, it is regarded as a chemical uncoupler.

Assay (III): Identification of chemical uncouplers that increase energy expenditure *in vivo*

The effect of the chemical uncouplers on energy expenditure (oxygen consumption) *in vivo* is determined by indirect calorimetry. Briefly, animals are placed in airtight chambers. Air is continuously led to and from the chambers. The gas concentrations of oxygen (O_2) and carbondioxide (CO_2) in the air led to and from the chambers (inlet and outlet air) are recorded and the consumption of O_2 and the production of CO_2 are calculated. Based on the amount of O_2 consumed and CO_2 produced, energy expenditure is calculated. Compounds which at a given dose increase whole body energy expenditure without obvious deleterious effects are deemed to be chemical uncouplers that increase energy expenditure.

CLAIMS

1. A compound according to formula I



[I]

wherein each R1 and R2 independently represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, haloalkyl, alkoxy, alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6, -OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;

R3 represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, alkoxy ,alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6, -OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;

R4 represents nitro, cyano, halogen, haloalkyl, -C(O)R6, -C(O)OR6, -$C(O)N(R6)_2$ or –$S(O)_2$OR6, $S(O)_n$R6, $S(O)_2N(R6)_2$, -$P(O)(OR6)_2$ or –$B(OR6)_2$;

R6 represents hydrogen or alkyl, aryl or heteroaryl, all of which may be substituted with one or more substituent selected from amongst hydroxyl, halogen, nitro and cyano;

n represents 0, 1 or 2;

R5 represents alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, all of which are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, carboxyl, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -NR7-C(O)R7, NR7-$S(O)_n$R7, -$(CH_2)_p$-N(R7)(R8) and phenyl, said phenyl being optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, nitro, O-R13, -$S(O)_n$R11, -O-C(O)R11, -C(O)-O-R11, -C(O)-R11 -C(O)-N(R11)(R12), -N(R11)(R12), -$(CH_2)_p$-N(R11)-C(O)-R12, -B(OR11)(OR12), -$(CH_2)_p$-O-R11, -$(CH_2)_p$-N(R11)(R12) ;

R7 and R8 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, dialkylether, cycloalkyl, heterocyclyl or phenyl, wherein said phenyl and heterocyclyl are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyl, hydroxyalkyl, cyano, nitro, -N(R9)(R10) and –$(CH_2)_p$-N(R9)(R10);

R9 and R10 independently represent hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl or cycloalkyl;

or R4 and R5 together with the atoms to which they are attached constitute a 5, 6, 7 or 8 membered ring, which may be saturated, either partly or fully or unsaturated, and wherein said ring is optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano and nitro;

each R11 and R12 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl or phenyl;

R13 represents haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalyl;

p represents 0, 1 or 2;

with the proviso that if R5 represents phenyl, then said phenyl is substituted, however not by fluor or trifluoromethyl; and with the proviso that R5 does not represents cyanomethyl; and with the further proviso that if R5 is thienyl or pyridyl, then said thienyl or pyridyl is substituted;

and pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof.

2. A compound according to claim 1, wherein each R1 and R2 are independently selected from the list consisting of alkyl, aryl, heteroaryl, halogen, nitro, -C(O)OR6, -$S(O)_2$OR6, wherein R6 is as defined in claim 1.

3. A compound according to claim 2, wherein each R1 and R2 independently represent alkyl, halogen or nitro.

4. A compound according to claim 3, wherein each R1 and R2 independently represent C_{1-6}alkyl.

5. A compound according to claim 4, wherein R1 and R2 both represent tert.-butyl, butyl, isopropyl or methyl.

6. A compound according to claim 2, wherein each R1 and R2 independently represent nitro.

7. A compound according to claim 2, wherein R1 and R2 independently represent chloro, bromo or iodo.

8. A compound according to any of claims 1-7, wherein R3 represents hydrogen, alkyl, alkenyl, alkynyl, alkoxy or alkylamino.

9. A compound according to any of claims 8, wherein R3 is C_{1-4}alkyl

10. A compound according to any of claims 8, wherein R3 is methyl.

11. A compound according to any of claims 1-10, wherein R4 represents nitro, cyano, -C(O)R6, -C(O)OR6, -C(O)N(R6)$_2$, –S(O)$_2$OR6 or S(O)$_n$R6, S(O)$_2$N(R6)$_2$, wherein R6 is as defined in claim 1, and n represents 1 or 2.

12. A compound according to claim 11, wherein R4 represents nitro.

13. A compound according to claim 11, wherein R4 represents cyano.

14. A compound according to claim 11, wherein R4 represents -C(O)R6, wherein R6 is as defined in claim 1.

15. A compound according to claim 11, wherein R4 represents –C(O)OR6, wherein R6 is as defined in claim 1.

16. A compound according to claim 11, wherein R4 represents –C(O)N(R6)$_2$, wherein R6 is as defined in claim 1

17. A compound according to claim 11, wherein R4 represents –S(O)$_2$OR6, wherein R6 is as defined in claim 1.

18. A compound according to claim 11, wherein R4 represents –S(O)$_n$R6, wherein R6 is as defined in claim 1, and n represents 1 and 2.

19. A compound according to claim 11, wherein R4 represents –S(O)$_2$N(R6)$_2$, wherein R6 is as defined in claim 1.

20. A compound according to any of claims 1-10, wherein R4 and R5 together with the atoms to which they are attached constitute a 5 or 6 membered ring, which may be saturated, either partly or fully, or unsaturated, and wherein said ring is optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano and nitro.

21. A compound according to claim 20, wherein R4 and R5 together with the atoms to which they are attached constitute a ring selected from the list consisting of [1,3]Dithiolane 1,1,3,3-tetraoxide, 1,1-Dioxo-tetrahydro-1-thiophen-3-one, 1,1-Dioxo-thiazolidine-4-one, 1,1-Dioxo-thiomorpholine-3-one tetrahydrothiopyran-1,1-dioxide or tetrahydrothiophen-1,1-dioxide, all of which are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano and nitro.

22. A compound according to any of claims 1-19, wherein R5 represents alkyl, aryl, heteroaryl, heterocyclyl, all of which are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -$(CH_2)_p$-N(R7)(R8), -NR7-C(O)R7, NR7-$S(O)_n$R7, wherein R7, R8 and p are as defined in claim 1.

23. A compound according to claim 22, wherein R5 represents alkyl, optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -$(CH_2)_p$-N(R7)(R8), -NR7-C(O)R7, NR7-$S(O)_n$R7,wherein R7, R8 and p are as defined in claim 1.

24. A compound according to claim 22, wherein R5 represents aryl, optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, carboxyl, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -$(CH_2)_p$-N(R7)(R8), -NR7-C(O)R7, NR7-$S(O)_n$R7, wherein R7, R8 and p are as defined in claim 1.

25. A compound according to claim 22, wherein R5 represents heteroaryl, optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -$(CH_2)_p$-N(R7)(R8), -NR7-C(O)R7, NR7-$S(O)_n$R7,wherein R7, R8 and p are as defined in claim 1.

26. A compound according to claim 22, wherein R5 represents heterocyclyl, optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, haloalkyl, -O-R7, -S(O)$_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -(CH$_2$)$_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -(CH$_2$)$_p$-O-R7, -(CH$_2$)$_p$-N(R7)(R8), -NR7-C(O)R7, NR7-S(O)$_n$R7,wherein R7, R8 and p are as defined in claim 1.

27. A compound according to claim 22, wherein R5 represents methyl or 2-propanyl, and said substituents are selected from the list consisting of halogen, hydroxyl, cyano, nitro, -C(O)-O-R7, -C(O)-N(R7)(R8), wherein R7 and R8 are as defined in claim 1.

28. A compound according to claim 22, wherein R5 represents phenyl substituted with one or more substituients selected from the list consisting of alkyl, halogen, hydroxyl, nitro, carboxyl, haloalkyl, -O-R7, -S(O)$_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -(CH$_2$)$_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -(CH$_2$)$_p$-O-R7, -(CH$_2$)$_p$-N(R7)(R8), -NR7-C(O)R7, NR7-S(O)$_n$R7,wherein R7, R8 and p are as defined in claim 1.

29. A compound according to claim 28, wherein said substituents are selected from the list consisting of chloro, hydroxyl, cyano, carboxyl, nitro, NR7R8, -O-R7, C(O)-R7, -C(O)-O-R7, -C(O)-N(R7)(R8), -NR7-C(O)R7, NR7-S(O)$_n$R7,wherein R7 and R8 are as defined in claim 1.

30. A compound according to claim 28, wherein said substituents are selected from amongst chloro, carboxyl, nitro, trifluoromethoxy, N,N-bis(2-methoxy-ethyl)-carbonyl, dimethylaminecarbonyl, N,N-bis(2-hydroxypripyl)-carbonyl, 4-metyl-piperazinyl-carbonyl, 2-hydroxy-ethylamine-carbonyl, 2,6-dimethyl-4-morpholinyl-carbonyl, 4-morpholinyl-carbonyl and -NH$_2$.

31. A compound according to claim 25, wherein R5 represents a heteroaryl selected from the list consisting of pyridyl and imidazolyl, optionally substituted with a substituent selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, haloalkyl, -O-R7, -S(O)$_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -(CH$_2$)$_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -(CH$_2$)$_p$-O-R7, -(CH$_2$)$_p$-N(R7)(R8), -NR7-C(O)R7, NR7-S(O)$_n$R7,wherein R7, R8 and p are as defined in claim 1.

32. A compound according to claim 31, wherein said substituents are selected from the list consisting of fluoro, chloro, methyl, hydroxyl, cyano, nitro, -C(O)-O-R7, -C(O)-N(R7)(R8), wherein R7 and R8 are as defined in claim 1.

33. A compound according to claim 26, wherein R5 represents a heterocyclyl selected from the list consisting of piperidinyl, morpholinyl, piperazinyl, tetrahydrofuranyl, optionally substituted with a substituent selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -$(CH_2)_p$-N(R7)(R8), -NR7-C(O)R7, NR7-$S(O)_n$R7, wherein R7, R8 and p are as defined in claim 1.

34. A compound according to claim 33, wherein said substituents are selected from the list consisting of of fluoro, chloro, hydroxyl, cyano, nitro, -C(O)-O-R7, -C(O)-N(R7)(R8), wherein R7 and R8 are as defined in claim 1.

35. A compound according to any of claims 1-34, wherein R7 and R8 independently represent hydrogen, alkyl, haloalkyl, hydroxyalkyl or phenyl.

36. A compound according to any of claims 1-35, wherein R9 and R10 independently represent hydrogen, alkyl, haloalkyl or hydroxyalkyl.

37. A compound according to any of claim 1-36, wherein R11 and R12 independently represent hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl or C_{1-6}hydoxyalkyl.

38. A compound according to claim 37, wherein R11 and R12 independently represent hydrogen, methyl, ethyl, trifluoromethyl, hydroxymethyl or 2-hydroxyethyl.

39. A compound according to any of claim 1-38, wherein R13 represents C_{1-6}alkyl, C_{1-6}haloalkyl or C_{1-6}hydroxyalkyl.

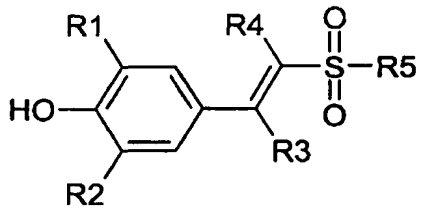
40. A compound according to claim 39, wherein R13 represents methyl, ethyl, trifluoromethyl, hydroxymethyl or 2-hydroxyethyl.

41. A compound according to any of claims 1-40, wherein n is 2.

42. A compound according to any of claims 1-41, wherein p is 1

43. A compound according to claim 1 selected from the list consisting of
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-methanesulfonyl-acrylonitrile;
(E)-2-(4-Chloro-benzenesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile;
(E)-2-(4-Chloro-benzenesulfonyl)-3-(4-hydroxy-3-nitro-phenyl)-acrylonitrile;
(E)-3-(4-Hydroxy-3-nitro-phenyl)-2-methanesulfonyl-acrylonitrile;
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(1-methyl-1H-imidazole-2-sulfonyl)-acrylonitrile;
(E/Z)-2-(4-Chloro-benzenesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-but-2-enenitrile;
(E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-benzoic acid;
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(4-nitro-benzenesulfonyl)-acrylonitrile;
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(4-trifluoromethoxy-benzenesulfonyl)-acrylonitrile;
(E)-3-(3-tert-Butyl-4-hydroxy-5-nitro-phenyl)-2-(4-chloro-benzenesulfonyl)-acrylonitrile;
(E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N,N-bis-(2-methoxy-ethyl)-benzamide;
(E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N,N-dimethyl-benzamide;
(E)-4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N,N-bis-(2-hydroxy-propyl)-benzamide;
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-[4-(4-methyl-piperazine-1-carbonyl)-benzenesulfonyl]-acrylonitrile;
(E)- 4-[3-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-prop-1-ene-2-sulfonyl]-N-(2-hydroxy-ethyl)-benzamide;
(E)- 3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-[4-(2,6-dimethyl-morpholine-4-carbonyl)-benzenesulfonyl]-acrylonitrile;
(E)- 3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-[4-(morpholine-4-carbonyl)-benzenesulfonyl]-acrylonitrile;
(E)-2-(4-Amino-benzenesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile;
(E)-2-[2-Cyano-1-(3,5-di-tert-butyl-4-hydroxy-phenyl)-ethenesulfonyl]-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile;
(E)-2-(4-Chloro-phenylmethanesulfonyl)-3-(3,5-di-tert-butyl-4-hydroxy-phenyl)-acrylonitrile;
(E)-3-(3,5-Di-tert-butyl-4-hydroxy-phenyl)-2-(propane-2-sulfonyl)-acrylonitrile.

44. A method of treating obesity, type 2 diabetes, dyslipidemia, hypertension, gallbladder diseases, preventing weight gain or maintaining a weight loss, wherein the method comprises administering to a patient in need thereof a therapeutically effective amount of a compound according to formula I



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wherein each R1 and R2 independently represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, haloalkyl, alkoxy, alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6, -OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;

R3 represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, alkoxy ,alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6, -OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;

R4 represents nitro, cyano, halogen, haloalkyl, -C(O)R6, -C(O)OR6, -$C(O)N(R6)_2$ or –$S(O)_2$OR6, $S(O)_n$R6, $S(O)_2N(R6)_2$, -$P(O)(OR6)_2$ or –$B(OR6)_2$;

R6 represents hydrogen or alkyl, aryl or heteroaryl, all of which may be substituted with one or more substituent selected from amongst hydroxyl, halogen, nitro and cyano;

n represents 0, 1 or 2;

R5 represents alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, all of which are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, carboxyl, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -NR7-C(O)R7, NR7-$S(O)_n$R7, -$(CH_2)_p$-N(R7)(R8) and phenyl, said phenyl being optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, nitro, O-R13, -$S(O)_n$R11, -O-C(O)R11, -C(O)-O-R11, -C(O)-R11 -C(O)-N(R11)(R12), -N(R11)(R12), -$(CH_2)_p$-N(R11)-C(O)-R12, -B(OR11)(OR12), -$(CH_2)_p$-O-R11, -$(CH_2)_p$-N(R11)(R12) ;

R7 and R8 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, dialkylether, cycloalkyl, heterocyclyl or phenyl, wherein said phenyl and heterocyclyl are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyl, hydroxyalkyl, cyano, nitro, -N(R9)(R10) and –$(CH_2)_p$-N(R9)(R10);

R9 and R10 independently represent hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl or cycloalkyl;
or R4 and R5 together with the atoms to which they are attached constitute a 5, 6, 7 or 8 membered ring, which may be saturated, either partly or fully or unsaturated, and wherein said ring is optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano and nitro;
each R11 and R12 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl or phenyl;
R13 represents haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalyl;
p represents 0, 1 or 2;
and pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof, optionally in combination with other therapeutically active compounds, wherein said other compound is being administered concomitantly or sequentially.

45. The method according to claim 44, wherein disease is selected from amongst type 2 diabetes, dyslipidemia, hypertension and gallbladder diseases, and wherein the patient is obese.

46. A method according to claim 44, wherein the disease is obesity.

47. A method according to claim 44 for prevention of weight gain or maintaining a weight loss.

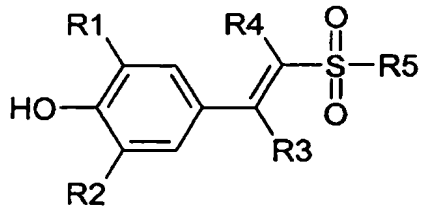
48. A method of treating obesity, atherosclerosis, hypertension, type 2 diabetes, dyslipidemia, coronary heart disease, osteoarthritis, gallbladder diseases, endometerial, breast, prostate, colon cancer, preventing of weight gain or maintaining a weight loss, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any of claims 1-43, optionally in combination with other therapeutically active compounds, wherein said other compound is being administered either concomitantly or sequentially.

49. A method according to claim 48, wherein disease is selected from amongst type 2 diabetes, dyslipidemia, hypertension and gallbladder diseases, and wherein the patient is obese.

50. A method according to claim 48, wherein the disease is obesity.

51. A method according to claim 48 for preventing weight gain or maintaining a weight loss.

52. Use of a compound of formula I



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wherein each R1 and R2 independently represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, haloalkyl, alkoxy, alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6, -OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;

R3 represents hydrogen, nitro, cyano, halogen, alkyl, alkenyl, alkynyl, alkoxy ,alkylamino, -C(O)OR6, -$S(O)_2$OR6, -$S(O)_n$R6, -OC(O)R6, -NHC(O)R6 or -$N(C(O)R6)_2$;

R4 represents nitro, cyano, halogen, haloalkyl, -C(O)R6, -C(O)OR6, -$C(O)N(R6)_2$ or –$S(O)_2$OR6, $S(O)_n$R6, $S(O)_2N(R6)_2$, -P(O)$(OR6)_2$ or –$B(OR6)_2$;

R6 represents hydrogen or alkyl, aryl or heteroaryl, all of which may be substituted with one or more substituent selected from amongst hydroxyl, halogen, nitro and cyano;

n represents 0, 1 or 2;

R5 represents alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, all of which are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano, nitro, carboxyl, haloalkyl, -O-R7, -$S(O)_n$R7, -O-C(O)R7, -C(O)-O-R7, -C(O)-R7, -C(O)-N(R7)(R8), -N(R7)(R8), -$(CH_2)_p$-N(R8)-C(O)-R7, -B(OR7)(OR8), -$(CH_2)_p$-O-R7, -NR7-C(O)R7, NR7-$S(O)_n$R7, -$(CH_2)_p$-N(R7)(R8) and phenyl, said phenyl being optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyalkyl, cyano, nitro, O-R13, -$S(O)_n$R11, -O-C(O)R11, -C(O)-O-R11, -C(O)-R11 -C(O)-N(R11)(R12), -N(R11)(R12), -$(CH_2)_p$-N(R11)-C(O)-R12, -B(OR11)(OR12), -$(CH_2)_p$-O-R11, -$(CH_2)_p$-N(R11)(R12) ;

R7 and R8 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, dialkylether, cycloalkyl, heterocyclyl or phenyl, wherein said phenyl and heterocyclyl are optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, haloalkyl, hydroxyl, hydroxyalkyl, cyano, nitro, -N(R9)(R10) and –$(CH_2)_p$-N(R9)(R10);

R9 and R10 independently represent hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, hydroxyalkyl or cycloalkyl;
or R4 and R5 together with the atoms to which they are attached constitute a 5, 6, 7 or 8 membered ring, which may be saturated, either partly or fully or unsaturated, and wherein said ring is optionally substituted with one or more substituents selected from the list consisting of alkyl, halogen, hydroxyl, cyano and nitro;
each R11 and R12 independently represent hydrogen, haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalkyl or phenyl;
R13 represents haloalkyl, hydroxyalkyl, alkyl, alkenyl, alkynyl, cycloalyl;
p represents 0, 1 or 2;
and pharmaceutically acceptable salts, solvates, hydrates and prodrugs thereof, optionally in combination with other therapeutically active compounds, in the manufacture of a medicament for the treatment of obesity, type 2 diabetes, dyslipidemia, hypertension, gallbladder diseases, for maintaining a weight loss or for the prevention of weight gain.

53. The use according to claim 52, wherein the disease is obesity.

54. The use according to claim 52, wherein the medicament is for prevention of weight gain or maintainig a weight loss.

55. The use of a compound according to any of claims 1-43 in the manufacture of a medicament for the treatment of obesity, atherosclerosis, hypertension, type 2 diabetes, dyslipidemia, coronary heart disease, osteoarthritis, gallbladder diseases, endometerial, breast, prostate, colon cancer, preventing of weight gain, for the prevention of weight gain or for maintaining a weight loss.

56. A method of preventing ageing, damages to the heart tissue and neuronal tissue, the method comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any claims 1-43.

57. The use according to claim 55 wherein the disease is obesity

58. The use according to claim 55, wherein the medicament is for preventing weight gain of for maintaing weight loss.

59. The use of a compound according to any of claims 1-43 in the manufacture of a medicament for the prevention of ageing, damages to heart tissue or neuronal tissue.

60. A compound according to any of claims 1-43 for use in therapy

61. A pharmaceutical composition comprising a copound according to any of claims 1-43, optionally in combination with another therapeutically active compound.

62. A compound according to claim 61 comprising a compound according to any of claims 1-43 in unit dosage.

ABSTRACT

Novel hydroxyl styrene sulfonyl derivatives are provided, useful in the treatment of obesity.